VOL. 17 NO. 3 JULY, 1960

BRITISH JOURNAL OF INDUSTRIAL MEDICINE

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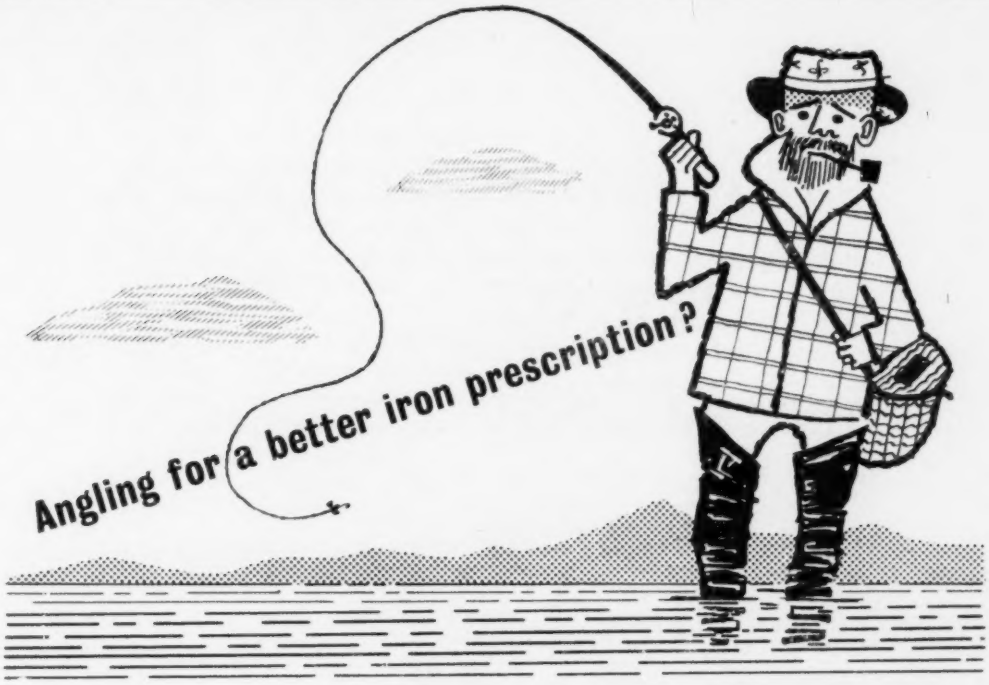

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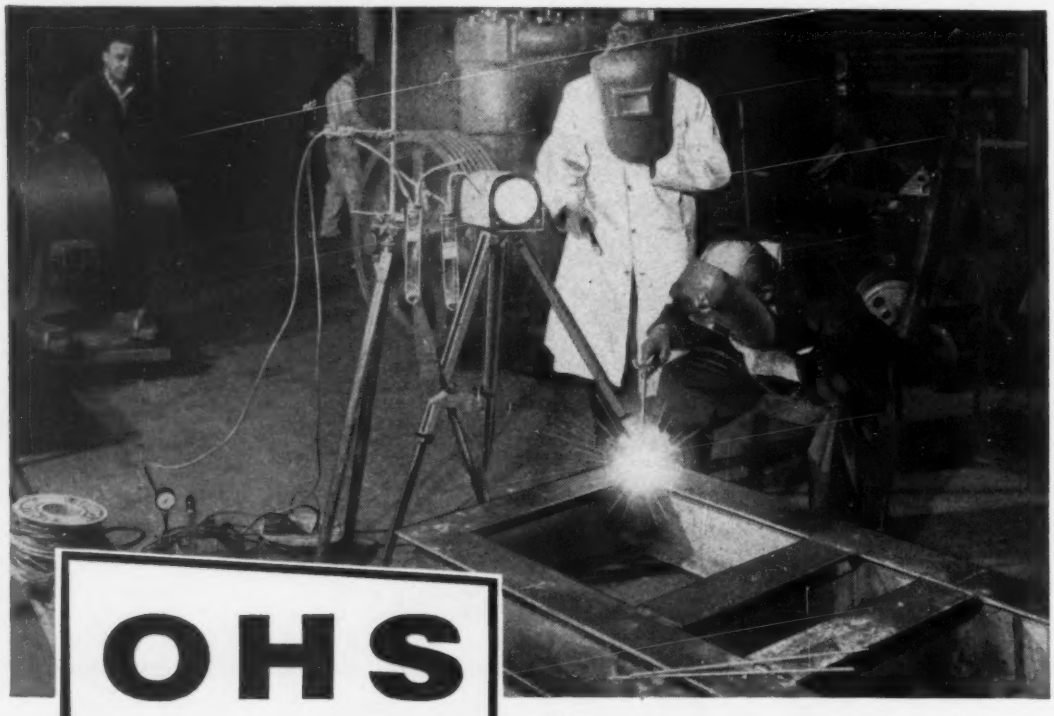

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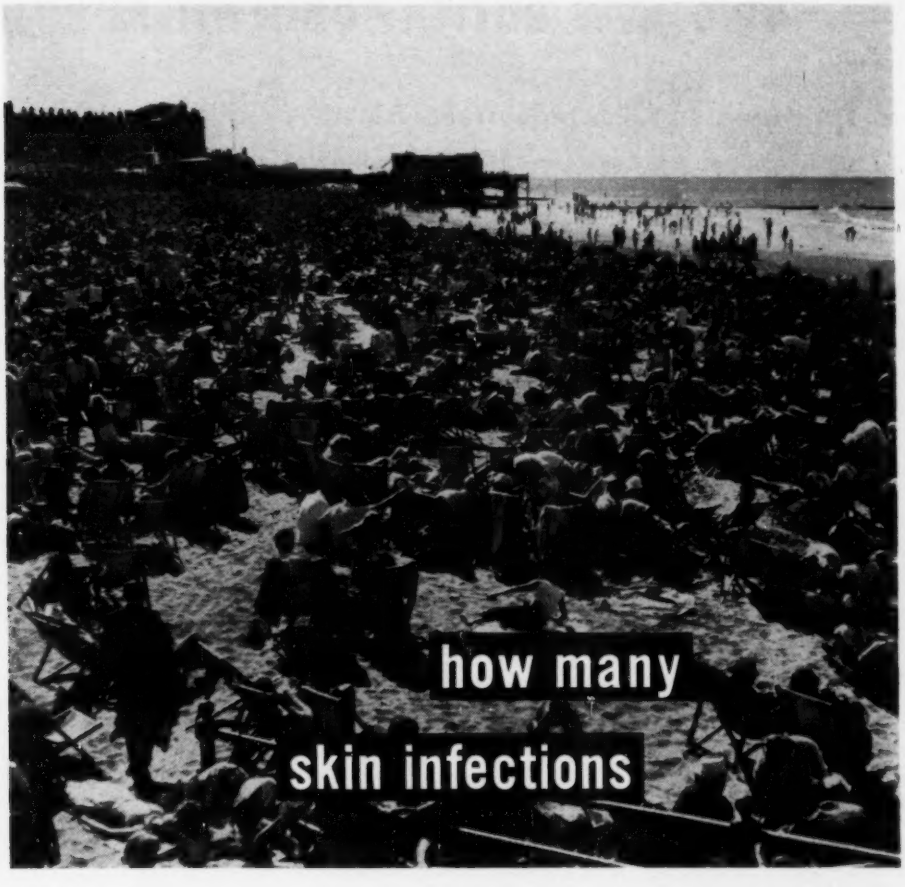

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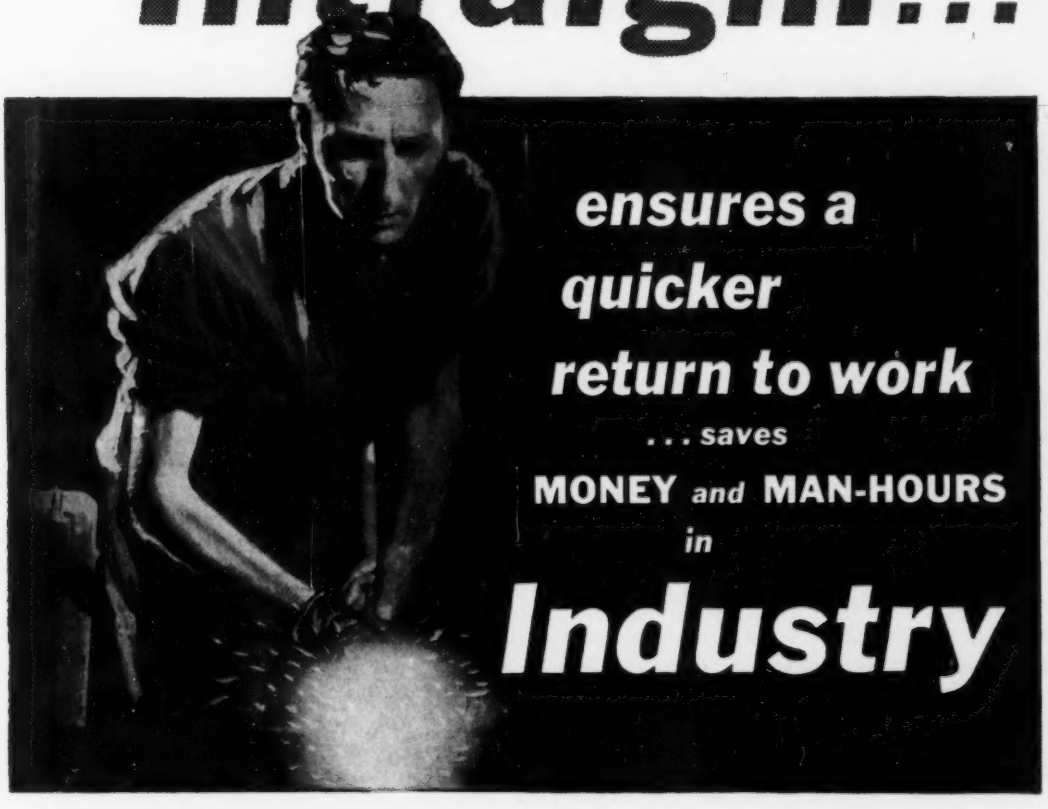

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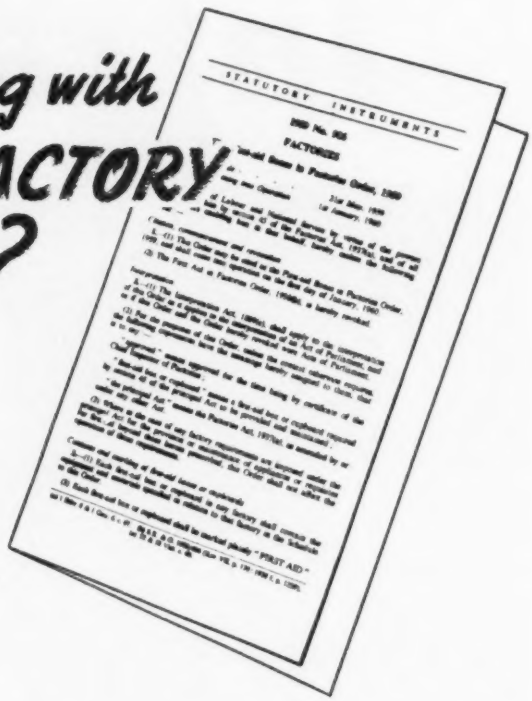

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DECOMPRESSION SICKNESS DURING CONSTRUCTION OF THE DARTFORD TUNNEL

BY

F. CAMPBELL GOLDING[1], P. GRIFFITHS[2], H. V. HEMPLEMAN[3], W. D. M. PATON[4], and D. N. WALDER[5]

A Report by the Dartford Decompression Sickness Panel of the Medical Research Council.

(RECEIVED FOR PUBLICATION MARCH 2, 1960)

A clinical, radiological and statistical survey has been made of decompression sickness during the construction of the Dartford Tunnel. Over a period of two years, 1,200 men were employed on eight-hour shifts at pressures up to 28 pounds per square inch (p.s.i.). There were 689 cases of decompression sickness out of 122,000 compressions, an incidence of 0·56%.

The majority of cases (94·9%) were simple "bends". The remainder (5·1%) exhibited signs and symptoms other than pain and were more serious. All cases were successfully treated and no fatality or permanent disability occurred. In two serious cases, cysts in the lungs were discovered. It is suggested that these gave rise to air embolism when the subjects were decompressed, and pulmonary changes may contribute more than hitherto believed to the pathogenesis of bends. Some other clinical features are described, including "skin-mottling" and an association between bends and the site of an injury. The bends rate is higher for the back shift (3 p.m. to 11 p.m.) and the night shift (11 p.m. to 7 a.m.) than for the day shift. In the treatment of decompression sickness it appears to be more satisfactory to use the minimum pressure required for relief of symptoms followed by slow decompression with occasional "soaks", than to attempt to drive the causative bubbles into solution with high pressures.

During the contract the decompression tables recently prescribed by the Ministry of Labour were used. Evidence was obtained that they could be made safer, and that the two main assumptions on which they are based (that sickness will not occur at pressures below 18 p.s.i., and that a man saturates in four hours) may be incorrect. It is desirable to test tables based on 15 p.s.i. and eight-hour saturation. The existence of acclimatization to pressure was confirmed; it is such that the bends rate may fall in two to three weeks to 0·1% of the incidence on the first day of exposure. Acclimatization is lost again, with a "half-time" of about seven days, if a man is away from work.

A study of bone damage in compressed air work has been started. In certain radiographs, abnormalities have been seen which may represent an early stage of caisson disease of bone.

The new tunnel between Kent and Essex under the Thames at Dartford is part of a four miles road link between A2, the London-Rochester road, and A13, the Barking-Southend road. It is situated 14 miles down river from the Blackwall Tunnel, until now the most easterly point at which it has been possible to cross the Thames by road. The river at Dartford is half a mile wide, so that the total length of the tunnel, including the sloping approaches at each end, will be approximately one mile. The tunnel lies about 20 ft. below the existing bed of the river in strata which consist of soft blue peaty clay overlying gravel which in turn overlies solid chalk. The preliminary pilot tunnel was completed in 1938, and the present contract for the full tunnel was let in 1956. It has an internal diameter of 28 ft. 2 in. and will accommodate two 10 ft. 6 in. traffic lanes with 16 ft. headroom, and be able to take double decker buses.

When constructing such tunnels, situated only a short distance underneath the river bed, it is necessary to use compressed air within the workings in order to keep out the water which would otherwise percolate through the surrounding strata and flood the tunnel. The pressure required to keep the tunnel

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[5] University Department of Surgery, Newcastle on Tyne.

dry varies according to the type of strata through which the tunnel is passing, and also with the depth of the river which at this point is tidal. In this project compressed air at pressures up to 28 pounds per square inch (p.s.i.) has been necessary.

The use of compressed air results in exposing the men who build the tunnel to the risk of decompression sickness. The risk can be minimized by taking certain precautions which have been laid down by the Minister of Labour and National Service in the Work in Compressed Air Special Regulations, 1958.

In spite of adherence to the prescribed precautions, however, a number of cases of decompression sickness still occur, and it is because of this that the present investigation has been carried out.

Arrangement of Workings

First two vertical shafts were sunk, one on each bank of the river, 2,832 ft. apart. From both of these, tunnelling was then begun towards the centre of the river.

A few months before these under-river tunnels from the two sides met, tunnelling under compressed air was started in a landward direction from the bottom of the Kent shafts, working towards the surface portal; about 200 ft. had been completed at the time of the junction.

All this work has had to be carried out in compressed air, which was first used on the Kent side in April 1957, and on the Essex side in September 1957. Owing to the slightly different nature of the ground on the two sides, pressures up to 28 p.s.i. have been used on the Kent side, but only up to 21 p.s.i. on the Essex side.

About six months before the tunnel across the river was completed, the pressure on the two sides was equalized.

Decompression Air Locks.—In order to get men and materials in and out of the tunnel whilst maintaining the pressure within, it was necessary to build air locks at both entrances to the workings. These air locks were situated at the bottom of the shafts in a short access tunnel; on each side of the river there was a man lock 12 ft. diameter by 33 ft. long (this was fitted with benches and could hold 50 men), and a material lock 7 ft. diameter by 28 ft. long. Heaters (two of 5 Kw. capacity) were fitted in the man lock to minimize discomfort when the temperature suddenly fell during the rapid phase of decompression. The locks were at all times controlled by a trained lock keeper, who was also responsible for keeping records of all persons entering and leaving the tunnel and ensuring that they received the correct decompression.

Medical Air Locks.—On each side of the river, situated at the medical centres, each within 100 yards of the top of the shafts, were two medical recompression chambers (each 7 ft. diameter and 14 ft. long). They were fully equipped with air lock entrances so that the doctor in charge and medical attendants could enter and leave during a recompression if it was necessary to examine or treat the patient, and so that food, books and other things could be passed in and out without interfering with the recompression.

Population at Risk and Working Shifts.—Over a period of two years (April, 1957 to April, 1959) 1,200 men have worked in compressed air on this contract, with between 250 and 320 on the active list at any one time. This has involved 122,000 compressions, of which 119,000 were at pressures over 16 p.s.i. Of the men, 1,060 were shift workers and 140 non-shift workers.

Throughout the duration of the compressed air work, a shift system has been in operation. Three shifts of approximately 25-30 men per shift are worked during the 24 hours, the men spending eight hours in the compressed air, followed by whatever period of time is necessary in the man lock to ensure proper decompression under the prevailing circumstances. In addition to the shift workers, there was a group of men (engineers, electricians, carpenters, fitters) entering and leaving the tunnel to perform tasks, the duration of which did not coincide with that of the regular shifts, who also had to be decompressed according to their exposure to compressed air.

Clinical Data

Definition.—It is first necessary to define what, for the purposes of this paper, should be regarded as decompression sickness. Many men suffer minor pains ("niggles") after decompression but these are too indefinite for quantitative study. Therefore only those cases with symptoms sufficiently severe to bring the man back for treatment have been counted as decompression sickness, and they were, in fact, always recompressed.

Classification of Cases.—There were 685 cases of decompression sickness. It was found that they could be divided into two types: Type 1, or simple "bends", which accounted for 650 of the total and Type 2, more serious and more complicated, of which there were 35.

TYPE 1 CASES.—In these the complaint was one of pain, usually described as being in or around a joint. In 85% the lower limbs only were affected; in 7%, upper limbs only; in 8% both upper and

lower limbs. The pain varied in intensity from a "nagging ache" to a very severe pain. It started on the average about three hours after decompression, but the time of onset varied considerably, from immediately after decompression to 12 hours later. Ninety-two per cent of the cases had worked shifts of eight hours or longer; 3% had worked for four hours only.

About half the cases responded quickly to recompression, but the remainder needed to be kept above working pressure for periods up to one hour before relief of pain was obtained. The most difficult case was that of a miner (Case 499) who had to be recompressed 10 times in all before he obtained complete relief of pains in the shoulders. On 12 occasions men suffering from the bends went back to work in the tunnel, without first reporting for medical recompression, and were not relieved of their symptoms; they had to be brought out from the tunnel and recompressed to a higher pressure in the medical lock in order to get relief.

Sometimes there was a history of bruising, sprain, or excessive use of the part of the body in which the bends pain arose. In 29 cases out of 502 (6%), over a period of 19 months, the evidence was sufficiently definite to be entered on the case sheet. In one case (Case 288) a man bruised his head in the tunnel, causing a small haematoma. Ten hours after decompression he returned from his home to the medical centre (a journey of 25 miles) with acute pain in the haematoma; on recompression the pain went at 10 p.s.i. and did not return. Among fitters, who frequently work in cramped or kneeling positions, the bends incidence was approximately 50% higher than among other workers. After a mild electric shock, one man (Case 348) suffered bends in the affected arm and shoulder. Some workers attributed their attacks to such causes as tiredness, lack of sleep or change of occupation in the tunnel involving the excessive use of muscles not "in training". Age does not seem to be important: as an example, two men who gave the wrong age and were found to be over 50 worked two years as labourers without trouble. The average age of Type 1 cases was 30 years.

TYPE 2 CASES.—These have been defined as patients presenting with symptoms other than pain or with abnormal physical signs. A summary of the presenting signs and symptoms in these cases is as follows: 26 with vertigo, 15 with signs of "shock" (pale, clammy, thready pulse, hypotension), six with visual symptoms, five with paralysis of limbs, five with epigastric pain, four with dyspnoea, three with speech defects, one with epileptiform attack, one with signs suggesting a cardiac lesion and one who collapsed and was unconscious on leaving the decompression lock. In addition to these 35 cases some men volunteered information about symptoms for which they had not requested treatment: 10 men reported brief attacks of "shortness of breath" on the way home, and two had visual symptoms within two hours of decompression.

The Type 2 cases always start early: six cases started either during the final stages of decompression or at its end; 26 cases started within one hour of the end of decompression. One case occurred six hours after decompression. The average time of onset was approximately 50 min. after decompression. The average age of the Type 2 cases was 36 years, somewhat higher than that of Type 1 cases.

No obvious predisposing cause was found; long exposure to pressure was not essential, for 11 cases had been exposed for five hours or less. In no case was the attack due to faulty decompression.

In general these cases reacted to therapeutic recompression more dramatically than did Type 1 cases; improvement usually began at comparatively low pressures, often considerably below working pressure (Table 1).

TABLE 1

COMPARISON OF SALIENT FEATURES OF TYPE 1 AND TYPE 2 CASES

	Type 1	Type 2
Symptoms	Limb or joint pain	Diverse
Latency of onset	0-12 hours from end of decompression Mean three hours	Before end of decompression to six hours after Mean 50 minutes
Response to decompression	Good but sometimes slow	Dramatic, sometime at quite low pressure
Age	Mean 30 years	Mean 36 years
Predisposing factors	Injury, fatigue, ischemia, long exposure	Lung cyst Long exposure not necessary
No. of cases	650	35

The following case histories illustrate some of the features mentioned:

Case Histories

Case 23.—This man, after working for eight hours at 21 p.s.i. fainted in the man lock during decompression with his shift, but recovered immediately. He was kept under observation for two hours and then allowed to go home apparently fit. Paralysis of legs and bladder came on gradually during the night, and it was 12 hours after decompression before treatment began. Relief of symptoms by recompression was successful, although a pressure much higher than working pressure was needed. Great difficulty was experienced in returning this patient to atmospheric pressure; despite the use of very slow decompression with periods of prolonged equilibration

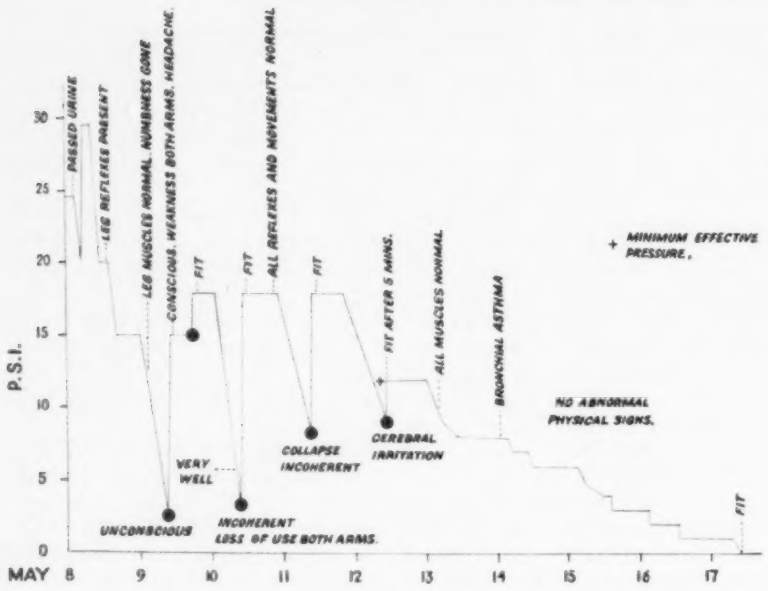

FIG. 1.—Diagram of the therapeutic recompression of Case 23, presenting with retention of urine and loss of reflexes in both legs, after an eight-hour shift at 21 p.s.i. The filled circles denote the pressure at which symptoms or signs recurred. (In medical lock 9½ days.)

at intermediate pressures (the so-called "soaks") and of oxygen inhalation, it was nine and a half days before he could be released from pressure without a return of symptoms. Fig. 1 shows his treatment diagrammatically. Especially remarkable was the manner in which paralysis of the lower or upper limbs returned within 2 lb. of atmospheric pressure in spite of lowering the pressure at a rate of only 1¼ lb. per hour, and later recurred with a rate three times slower. The only physical abnormality detected at subsequent medical examination was the cyst at the base of the right lung mentioned elsewhere in this paper.

Case 268.—An engineer aged 55 fell unconscious on leaving the man lock, after only three-quarters of an hour at 26 p.s.i. He was recompressed immediately in the man lock and kept at 26 p.s.i. When he recovered consciousness 20 minutes later he could move neither arms nor legs; all reflexes were exaggerated and plantar responses extensor. Thirty minutes later he was free of symptoms and had normal reflexes. He was very slowly decompressed and quickly transferred to the medical lock where further recompression and decompression treatment was completed. Both ear drums were damaged during the initial emergency recompression, but they healed quickly without disability. Subsequent investigation showed him to be a fit man, but radiological investigation of his chest revealed a cyst at the base of the right lung.

Case 341.—An engineer aged 48 collapsed with signs of "shock" 15 minutes after an exposure of one hour at 26 p.s.i. He recovered quickly on recompression and no other ill effects were detected. Later, a radiograph of his chest (AP) appeared normal.

Both these engineers had been exposed repeatedly to compressed air for many years without previous trouble.

Case 9.—A chargehand fitter aged 41 had "staggers", and was apparently cured by treatment in the medical lock. One hour later, while still under observation, he collapsed unconscious, with a pulse rate of 40. Within five minutes of recompression he was conscious and well, with a pulse rate of 78, and no further trouble was experienced. With this man, also, an AP chest radiograph was normal.

Skin Mottling.—An interesting sign seen in some subjects after decompression is the occurrence of a purplish patchy discolouration of the skin, known as "mottling" (Fig. 2). This disappears on local pressure, returning when pressure is released. The area most commonly affected was the upper abdomen but occasionally it was seen spreading to the back and down the limbs.

Faint mottling was often seen over the upper abdomen during routine inspection, but unless associated with symptoms, was ignored. Some authorities consider the occurrence of skin mottling to be an indication of grave prognostic significance; and therefore any man with severe mottling, with or without other symptoms, was either forbidden to work in compressed air, or limited as to time and pressure.

Twenty-two men showed extensive mottling and of these, 15 were obese. In 15 cases, there were other symptoms requiring recompression; in seven cases, the men reported the mottling but had no symptoms other than skin irritation. One fitter (Case 126) who used a hammer for four hours at 24 p.s.i. within an hour of decompression had a

FIG. 2.—Photograph of mottling of the trunk after normal decompression of a shift worker from a pressure of 26 p.s.i.

symptomless deep purple discolouration over the right shoulder and chest, covering almost exactly the muscles most used in hammering.

Cases Occurring among Men exposed to Pressures Less than 18 p.s.i.—Since bends are usually supposed to be rare at pressures less than 18 p.s.i., some details of those occurring at Dartford require mention. There were 45 cases, 41 being Type 1, and the remaining four Type 2. Table 2 shows the pressures at which they occurred. Of the Type 1 series, one man had worked only four hours; three others had worked 10 hours or more. The Type 2 cases had all worked eight-hour shifts.

TABLE 2

CASES OF DECOMPRESSION SICKNESS AT PRESSURES LESS THAN 18 p.s.i.

Pressure (p.s.i.)	Type 1 Cases	Type 2 Cases
16	—	1
16½	6	1
17	23	—
17½	12	2

The occurrence of cases, both non-serious and serious, at these low pressures, raised the question of the accuracy of the pressure gauges. All pressures were recorded on three separate large scale gauges which were calibrated regularly by the makers, Messrs. Elliott Bros. At no time were errors more than 0·5 p.s.i. detected and they were always such that the recorded pressure was higher than the true pressure.

Radiological Studies

The construction of a tunnel under the Thames at Dartford presented an opportunity to carry out a radiological survey on men working in compressed air. This was made possible by the loan of radiographic apparatus from the Royal Air Force and facilitated by the cooperation of the contractors. The apparatus was installed in the medical centre, close to the shaft when the tunnel was about half-way to completion. The original intention was to radiograph the limbs of those men who had suffered an attack of bends, in order to determine the incidence of aseptic necrosis in bone, but this objective was later extended to include some workers who had escaped a frank attack of bends but had had minor symptoms described as niggles, or had suffered from mottling of the skin. Coincident with this survey, two examples of severe decompression sickness were encountered. A radiograph of the chest showed that both men had lung cysts. At this time no relationship had been established, either by other investigators or by ourselves, between disease of the lungs and these major attacks, but after these events a radiograph of the chest was taken of all men starting to work in compressed air.

Bone and Joint Lesions.—The literature contains many examples of bone and joint lesions attributed to decompression sickness. Nearly all these were patients who attended hospital because they complained of symptoms. The extent to which bone changes occur without symptoms has hardly been explored. The lesions in bones and joints consist of sclerotic changes in the medulla which often terminate as "lakes" in the bone, and a varying degree of destruction of articular surfaces, the predominant feature being sclerosis. The radiology of aseptic necrosis has been described many times and does not require review here.

Radiographs were taken of the shoulders, hip joints and knee joints, including a large part of the diaphysis, in each case. In the early part of the survey only experienced compressed-air workers were examined, men who had had one or more attacks of bends. There were 83 men in this group and none of them complained of symptoms.

TABLE 3

BONE SCLEROSIS IN COMPRESSED AIR WORKERS

Age	Period of Employment in Compressed Air (years)	Maximum Pressure Worked (p.s.i.)	Number of Attacks of Bends Experienced	Radiological Findings: Sites of Sclerosis
43	22	40	6	Right shoulder upper shaft
61	31	40	Many	Femora lower shaft Tibiae upper shaft probably
40	12	40	3 attacks of staggers and chokes	Femora lower shaft Tibiae upper shaft probably Right humerus at joint
40	10	46	6	Right femur-joint at hip Left femur lower shaft probably
34	5	42	1	Right femur lower shaft Left femur doubtful lower shaft
43	8	40	7	Femora lower shaft Left humerus at joint Right humerus probably at joint
28	2	28	5	Femur upper shaft
37	1	28	None	Right humerus upper shaft
38	3	40	None	Left humerus joint
36	10	28	None	Right femur upper shaft
30	1½	28	5	Right femur—joint at hip
30	3½	28	2	Femora lower shaft Left femur—joint at hip
21	1½	28	1	Left femur at hip joint

An analysis of these 13 cases showed that the medulla of the shaft of long bones was affected in 19 instances, of which five were designated as highly probable, but not certain, involvement. The joints were involved in eight instances; in one of these the diagnosis might have been questioned. The films which were regarded as doubtful are not included. Of the 83 men who had had an attack of the bends, 10 had demonstrable changes in the bones. Of the 20 men who had not had an attack of bends, three showed demonstrable changes in bones.

Towards the end of the investigation it was decided to examine men who had never had an attack of bends, it being thought possible they might show radiological changes; it is already known that medullary infarcts, when the joint is unaffected, are symptomless. Unfortunately, as many workers had left, there was at this time only a small group of 20 men who had worked for varying periods in compressed air without an attack of bends. Of these men, three showed some evidence of early infarction (see Table 3). No comparable population exists from whom control radiographs could be obtained; but the lesions recorded are such as had never occurred in routine hospital radiological work.

It was expected that a routine antero-posterior film would give all the information that was required to establish a diagnosis. This expectation was based on the frank abnormalities which have been reported in the literature. It was soon realized that lateral films were necessary to confirm the diagnosis in many cases, since minor variations in texture were discovered which might have been disregarded without the lateral projection.

Two results emerged: (1) Labourers who have worked for years in compressed air, and are still working without symptoms, may show evidence of aseptic necrosis in bones and joints; (2) Aseptic necrosis may be found in the absence of a history of bends for which treatment has been sought.

Pulmonary disease.—In two men (Cases 23 and 268) lung cysts were found by radiological examination (Fig. 3). In Case 23, there were two thin-walled cavities in the right lower zone of the lungs, measuring 1·5 in. in diameter, and not containing fluid. In Case 268, there was a single cyst, again in the right lower zone, 1·5 in. diameter; it contained a fluid level, indicating that it communicated with a bronchus and that the bronchus was partly occluded.

Although it must be supposed that these cysts were the cause of the sickness of the two men the evidence is only circumstantial. The mechanism by which they could do so is sufficiently clear. A partial occlusion of a bronchus could become complete at any time. Should this occur during decompression, the cyst must expand when the ambient pressure falls. This would lead, at least, to an abnormal gas exchange through the wall of the cyst, and possibly to rupture of the wall and discharge of gas into venous channels. A process of this sort would account for the peculiarities of Case 23, especially the fact that the rate of lowering of pressure during the recompression had to be far slower than is needed in conventional therapeutic decompression. This is intelligible if the problem were the elimination of free gas from a closed cystic space, rather than the elimination of dissolved gas from a tissue perfused by circulating blood. But the problem remains as to why, if the men have had the cysts for some time, they did not encounter trouble earlier; or, if the cysts were a result of damage to the lung, how such well defined cavities were produced, quite unlike the rents observed with lungs burst by raised intrapulmonary pressures.

These pressure effects in the lung are analogous

to those which cause lesions in the middle ear when the Eustachian tube is blocked. The comparison suggests that complete blocking of minor bronchi in acute bronchitis or chronic bronchitis and emphysema might lead to decompression sickness and might even be a factor in the large variation of weekly bends incidence among labourers under constant working conditions. This would imply that patients with bronchitis and emphysema are not good risks for work in compressed air, and has prompted a further exploration of the radiological and physiological state of the respiratory tract in compressed air workers. A great advance in the prevention of decompression sicknesss, particularly of its major calamities, might be made if it were possible to radiograph the lungs of a patient in the recompression chamber during the attack.

Such cases present a therapeutic problem. In the first place, the cyst cavities, being organized structures, cannot be made to disappear by high pressure or by prolonged treatment, as can a bubble. Secondly, it is usually supposed that bubble formation will not occur in the body until a large pressure change is experienced, but in the event of occlusion of a bronchus small pressure changes are likely to cause trouble. It is advisable that in any atypical or serious case of decompression sickness the possibility of a cyst or of occlusion of a bronchus be borne in mind and two general principles followed: extremely slow rates of therapeutic decompression should be used and, should symptoms recur, no attempt must be made to dissolve a bubble by recompressing the patient to high pressures; the pressure should be raised just sufficiently high to relieve the symptoms. When this has been achieved, the slow decompression can be resumed.

FIG. 3a

FIG. 3a.—Chest radiograph of Case 23. There are two cysts, one partly concealed by the right border of the heart: no fluid levels.

FIG. 3b

FIG. 3b.—Chest radiograph of Case 268. There is a cyst in right lower zone, containing a fluid level.

Statistical Analysis of Some Factors in Decompression Sickness

The number of cases of decompression sickness per 100 compressions will be called the "bends percentage". Table 4 summarizes the general bends rate over the whole period of the contract.

TABLE 4

INCIDENCE OF DECOMPRESSION SICKNESS

Pressure (p.s.i.)	Compressions	Bends	%
Kent Side			
0-16 All exposures	530	nil	0
16-18 All exposures	810	7	0·86
18-28 Over 4 hours	55,900	576	1·03
Under 4 hours	14,500	7	0·05
Essex Side			
0-16 All exposures	1,320	nil	0
16-18 Over 4 hours	17,500	40	0·23
Under 4 hours	6,250	nil	0
18-21 Over 4 hours	16,800	47	0·28
Under 4 hours	5,900	nil	0
Caissons			
0-23 Up to 12 hours	2,400 (decanted)	8	0·33

For detailed analysis, the weekly bends incidence for the Kent side workings over the first 68 weeks of the contract was used. The incidence, plotted in Fig. 4a, varied considerably, from nil to 2·64%, with a modal value of 0·5-1·0%. It bore little direct relation to the pressure in the workings (Fig. 4b). The average bends percentage for the whole of this particular period, in this part of the workings where the tunnelling was hardest, was 0·98%. This is a very creditable figure for the earlier part of a contract; but there are indications that it could be improved.

Variation in Susceptibility.—It was obvious that some men have more than their share of bends. The frequency with which men were attacked is shown in Table 5. This shows the way in which a relatively small group of men are responsible for quite a large proportion of the bends. As an example, if the 12 men with five or more bends were to be eliminated then the total number of bends would fall to 310, and bring the average percentage over this 68-week period from 0·98% to 0·77%; if 43 men (about 4% of the working force) with three or more bends were eliminated, the bends incidence would be halved. A further point is that 20% of the total population of workmen had one or more attacks of the bends. Thus it is possible to judge the success of present procedures from contrasting points of view. For an individual worker the risk of an attack of bends at some time during his work in compressed air is quite high (20%); but from the medical aspect the bends percentage, *i.e.*, the number of bends per 100 compressions, is satisfactorily low (1%).

Decompression Schedule (as described in the Work in Compressed Air Special Regulations, 1958).

Although the present decompression procedure affords considerable protection against bends we obtained evidence that it could be usefully revised, as regards two fundamental assumptions on which the calculations are based.

(1) In preparing the official decompression tables it has been assumed that 18 p.s.i. represents a safe threshold pressure below which negligible trouble would occur. This turned out to be untrue. In the first few weeks on the Kent side, while the pressure was rising from 10 p.s.i. to 18 p.s.i., the average weekly incidence rose steadily to over 0·8% and eight cases of bends occurred. This was sufficiently serious to call for a modified decompression schedule; to provide increased protection the slow phase of all decompressions was lengthened to 10 minutes per lb. Men working at pressures from 16 to 18 p.s.i. were decompressed as though they had worked at 18 to 20 p.s.i. Even with this revised threshold pressure, 28 bends (0·2%) occurred in the Essex workings over a period of six months although the pressure never exceeded 17½ p.s.i. It appears, therefore, that even 16 p.s.i. is above the threshold pressure for absolute safety.

Another sign that the usual assumptions are inadequate appeared when the incidence on the Essex side was compared with that on the Kent side for a similar period; on the Kent side, the incidence was about four times greater, about 1·0%. It is true that the pressure was much higher on the Kent side; but if the decompression tables were properly constructed, the protection should be equal at all working pressures.

(2) In calculating the present decompression routine, it has been assumed that four hours at some pressure is sufficient to ensure full saturation of the relevant body tissues to that pressure. In the decompression tables this assumption gives rise to decompression times which increase as duration of work increases until a four-hour exposure is reached.

TABLE 5

DISTRIBUTION OF BENDS OVER 68-WEEK PERIOD ON KENT SIDE

Number of bends per man	0	1	2	3	4	5	6	7	8	20
Number of men	817	118	43	18	13	5	1	4	1	1
Number of bends per group	0	118	86	54	52	25	6	28	8	20

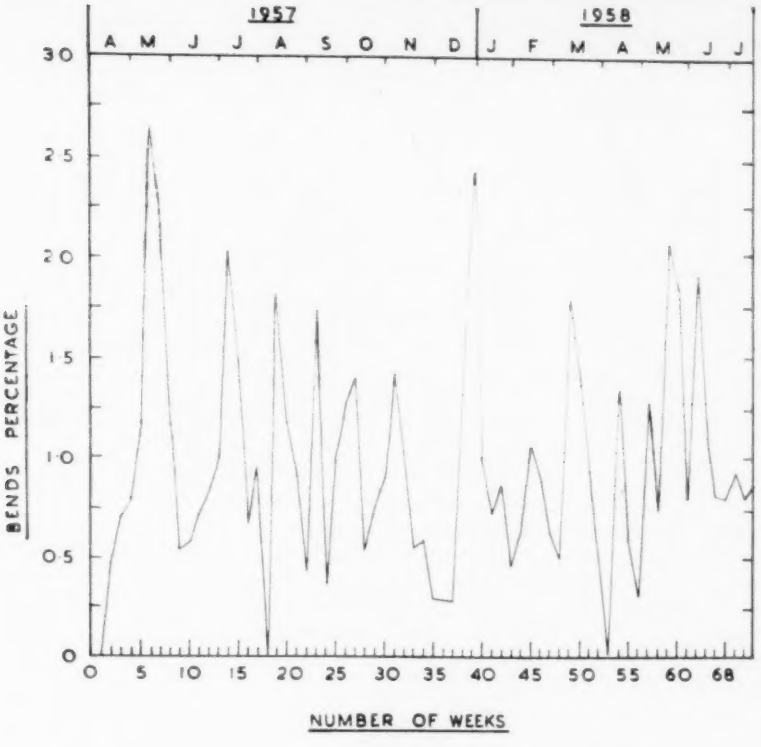

FIG. 4a.—Graph of the weekly bends percentage on the Kent side.

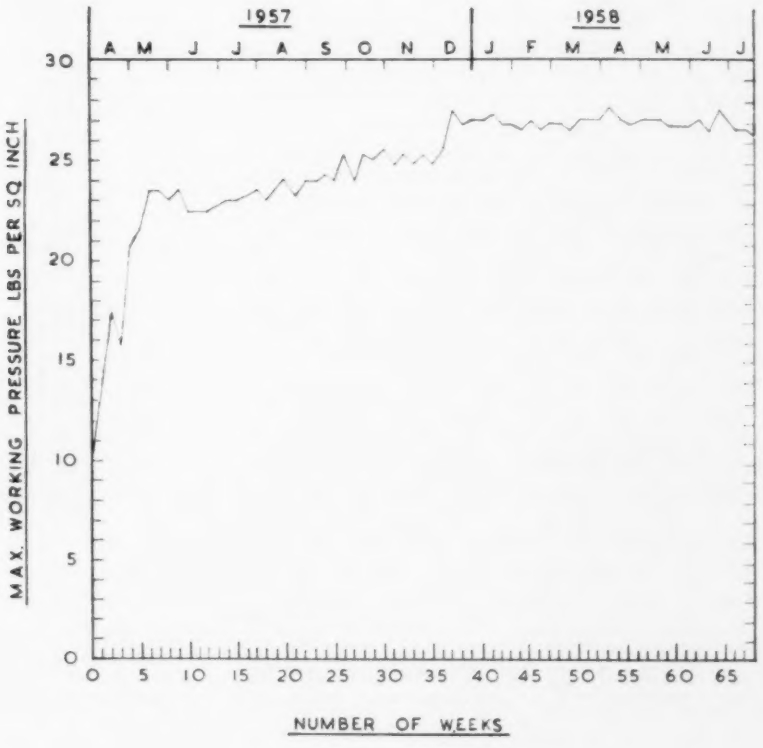

FIG. 4b.—Graph of the maximum weekly working pressure (p.s.i.).

TABLE 6

VARIATION IN BENDS INCIDENCE WITH NATURE AND DURATION OF WORKING PERIOD

	Day Shift (7 a.m.-3 p.m.)	Back Shift (3 p.m.-11 p.m.)	Night Shift (11 p.m.-7 a.m.)	Total
Number of compressions over four hours	12,943	7,905	8,174	29,022
Number of compressions under four hours	8,198	2,645	410	11,253
Bends percentage (over four hours)	1·13	1·78	1·28	1·35
Bends percentage (under four hours)	0·02	0·02	0·00	0·03
Overall percentage	0·70	1·34	1·22	0·98

All periods of work longer than four hours have, at present, the same decompression time. If this was a correct procedure, the risk of periods of work, four hours or less in duration, should be of the same order as periods of work greater than four hours duration. Table 6 shows an analysis of the experience over the 68-week period on the Kent side; it is quite clear ($p<0.001$) that the risk is far greater with the longer exposure.

This table also brings out two other important points. The group of men exposed for four hours or more constitute the shift working population; it can be seen that they carry the greatest part of the bends risk. Further, there is a distinct tendency for the back shift to be the most hazardous ($\chi^2 = 37$, d.f. $= 2$, $p<0.001$). This tendency persists even if the shift workers alone are considered ($\chi^2 = 16$, d.f. $= 2$, $p<0.001$).

Acclimatization.—The existence of a marked decline in bends incidence with the number of shifts worked was established in an earlier report (Paton and Walder, 1954). The present undertaking gave an opportunity to confirm and extend these findings. The ordinary shift workers proved to be an unsuitable group for this investigation; the reason was that the presence of alternative compressed air work in the district made it difficult to be certain that the new starters at Dartford were new starters at compressed air work. The employment of 22 steel erectors, who had never entered compressed air until they commenced work at Dartford, provided, however, a remarkable opportunity for examining this question. These men were all quite fit, and they were well used to the type of job which they performed in the tunnel. They were followed for a period of time of over one month, during which the pressure was relatively constant. The number of attacks of bends versus the number of shifts is shown in the histogram (Fig. 5). There is a large decline in the bends incidence with the passage of time; the data are well fitted ($r = 0.97$) by the regression line $\log_{10}$ (number of bends) $= 1.16 - 0.42$ (number of compressions) giving a half time of 7 ± 4 compressions ($p = 0.05$).

It was also found that working at low pressures for a few days does not appear to confer any measurable benefit on men subsequently introduced to higher pressures. This can be seen from Fig. 6 where a progressive rise of pressure caused an increase in the number of bends; but once the steady maximum level had been reached there was quite a marked fall in bends incidence very similar to that in Fig. 5, where no one had had previous experience of air work.

The confirmation of the existence of acclimatization to air work led naturally to the question of how long the acclimatization persisted when air work ceased. To answer this question the complete histories of a large number of men were scanned to see when an attack of bends occurred on returning to work after a period of absence. The week-ends gave a large number of two-day lapses in regular

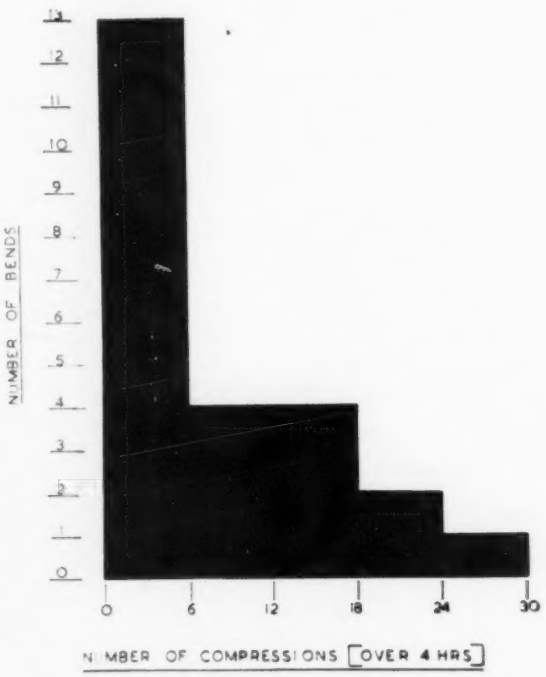

FIG. 5.—Graph of the number of bends occurring in a group of 22 steel erectors, for exposures over four hours, in relation to the number of compressions to which they had been exposed; showing the development of acclimatization.

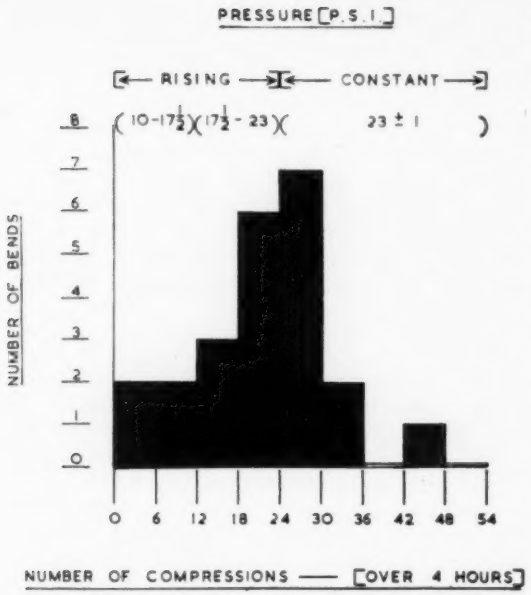
PRESSURE [P.S.I.]
RISING
CONSTANT
(10-17½)(17½-23)
23 ± 1
NUMBER OF BENDS
0 1 2 3 4 5 6 7 8
0 6 12 18 24 30 36 42 48 54
NUMBER OF COMPRESSIONS — [OVER 4 HOURS]

FIG. 6.—Graph of the number of bends occurring in relation to the number of compressions experienced, during a period when the pressure rose from 10 to 23 p.s.i., and then remained constant. Acclimatization did not begin until the pressure stabilized, showing that exposure to low pressures does not protect against exposure to higher pressures.

working, and holidays and strikes gave a large number of lapses of 10 days or over. Unfortunately, few figures accumulated for intermediate periods of time. Fig. 7 shows that whenever a man was away for a period exceeding 10 days then his chance of obtaining a bend on returning to work was very much greater than if he had been away for only two days. The two-day figure is represented by 14 bends and the over-10-day figure by 24 bends, the difference between them is highly significant. The intermediate points, whilst not contradicting the general trend do not permit any further quantitative statements to be made.

The existence of processes of acclimatization and "de-acclimatization" can now be seen to account for a great deal of the apparent randomness in the attacks of bends. The magnitude of the contribution of acclimatization and de-acclimatization may be judged by assuming that some procedure had been evolved to introduce new starters safely to compressed air work and to ensure that no bend occurred in the first three shifts after a period away from work of 10 days or more. In this eventuality the total number of bends over the 68-weeks period would drop to 170 and the overall percentage from 0·98% to 0·42%. The possibility of safely introducing men to higher pressures by first working them at lower pressures has already been shown to fail (Fig. 6). The time spent at the lower pressure appears to be quite irrelevant; thus there are nine cases of men who spent several months free from discomfort at 17 p.s.i. but when transferred to working at 27 p.s.i. had an attack of bends in the first few shifts at the new pressure. There remains the possibility of introducing men to compressed air working by gradually increasing the time worked at pressure. Since the half-time of the acclimatizing process is about seven days any such method would need to be quite prolonged in order to give useful protection. Unfortunately, there is no evidence from the present workings to indicate whether such a procedure would meet with success.

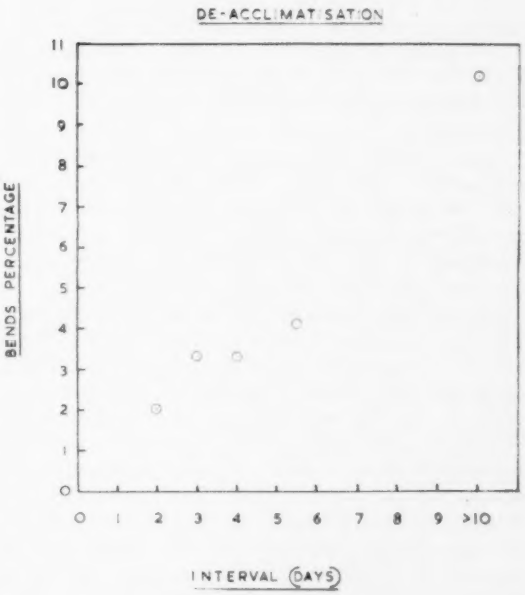

FIG. 7.—Graph of the increase in bends percentage against the duration of a period away from work under pressure.

Climatic Conditions.—During the construction of the Tyne Tunnel, Paton and Walder (1954) failed to find any connexion between the external climatic conditions prevailing and the bends rate. It was thought that the internal environment of the Dartford Tunnel should be investigated.

The most striking finding is the constancy of the internal environment of the tunnel. This appears to be quite independent of the external climatic conditions. Observations were made from September, 1957 to August, 1958 a period including

great changes in the outside weather conditions. Yet the air temperature ranged only from 55 to 69°F. and the relative humidity between 97% and 99%. Considerable difficulty was experienced in measuring the wind velocity in the tunnel, because Kata-thermometer readings are inaccurate when made in compressed air, but the movement of titanium tetrachloride clouds and soap bubbles in the tunnel suggested that the wind velocity was of the order of 5 ft./min. At first sight it is surprising that men can do hard and prolonged physical work in an environment which is 97% saturated but calculation of the "corrected effective temperature" shows this to be well within the accepted limits of comfort. No relationship could be demonstrated between the internal environment of the tunnel and the bends rate.

Methods of Treatment

All cases were treated by recompression; the methods used were modified during the course of the contract, and were adapted to the nature of the case.

Type 1 Cases.—The majority of cases were compressed to 2-3 lb. above the working pressure and, after being free of symptoms for 10 minutes were decompressed in the usual way, as though for an exposure of more than four hours. If the patient was not free of symptoms after one hour at 3 lb. above working pressure, a higher pressure was used. On two occasions it was necessary to use 10 lb. above working pressure. The pressure at which fast decompression ceased and the slow phase commenced was, in every case, based on the highest pressure to which the man had been exposed in the previous 24 hours—either in the working chamber or medical lock. With this decompression time, however, a third of the cases required one or more further recompressions. For all cases after the first 50, the slow phase of the decompression was therefore lengthened from 9 min./lb. to 15 min./lb.; even so one in 10 required further recompression.

In 56 cases the pressure was raised, not as just described, to a few pounds above working pressure, but only to the pressure required to make the patient symptom-free; after 10 minutes at this pressure, routine decompression was carried out. The average "minimum effective pressure" required was 8 lb. below working pressure. The results were very satisfactory, only one case requiring a second recompression. The use of the minimum effective pressure was also found satisfactory when recompressing a second time; in these cases the man was kept at the requisite pressure for half an hour before decompressing.

About 25% of the men had a "residual soreness" at the end of treatment. There is a marked difference between this soreness and the pain of "bends" and the patient is always aware of the difference. Heat treatment (exposure to the radiations of an infra-red lamp) was found to be beneficial for this residual soreness as also was the use of tablets of aspirin or tab. codein co., B.P. In all cases the patient was considered to be free from the pain of "bends" at the end of treatment. If it was considered that, because of time spent in medical lock under treatment, the man had had insufficient sleep since his last shift, he was advised to miss a shift.

Type 2 Cases.—All cases were treated by immediate recompression. Initial recompression was always to working pressure, higher pressures being used when necessary to remove symptoms. The "effective pressure" was maintained for half an hour after all signs and symptoms had gone before decompression was commenced. The decompression was slow, and the patient was recompressed at once if signs or symptoms returned. For the first four cases the rate of decompression was 10 min./lb. After the fourth case (23) a period of soaking of one to four hours at 12 or 15 lb. was added during the slow decompression. After the 19th case (306) a more prolonged course of treatment was used for all subsequent Type 2 cases. This treatment was as follows: The effective pressure was maintained for half an hour after all signs and symptoms had gone. The patient was then decompressed to 12 p.s.i. at 15 min./lb. and "soaked" (*i.e.*, maintained) at 12 lb. for four hours. Decompression was then continued at the rate of 1 lb. every half hour, "soaking" for one and a half hours at 8 lb., one hour at 4 lb., and one hour at 2 lb. Although this method may take 15-20 hours no additional recompressions have been necessary after its use. Any man who suffered a Type 2 attack of bends was either forbidden to go into compressed air again or strictly limited as to maximum permissible compression pressure and duration of exposure.

Discussion

In principle, decompression sickness should be a totally preventable disease. In fact, it is extremely difficult to eliminate. In assessing the incidence of sickness on this contract particular attention must be paid to two factors. The first is the number of compressions which take place at pressures where a risk exists. Often at the beginning of a working, only trivial pressures are used; yet recording each exposure as a "compression" may serve to lower enormously the overall bends rate. Without information as to the history of the pressure changes in the working, an overall bends rate can be almost

meaningless (see, for instance, Kooperstein and Schuman, 1957); it is desirable to know the rate for pressures above 16 or 18 p.s.i.; and, on large contracts, the number of deaths or of cases of permanent disability, are important. The second factor is that of shift length. A common safeguard, used especially in the United States, is to shorten the time spent by each shift in compressed air as pressure rises. Thus a regime may be used which consists, for instance, of two spells of one and a half hours each in compressed air separated by an interval of three hours, which is very wasteful of manpower, but appears safe. The incidence of bends has ranged from about 0·05% to 1% with this type of regime (Norrie, 1934; Boulton, 1942; Levy, 1922; Keays, 1909; Kooperstein and Schuman, 1957). Deaths and permanent paraplegia have still, however, been recorded.

It may be that a procedure of this sort offers advantages. But the recent regulations agreed by the Ministry of Labour and the Institution of Civil Engineers in this country lowered the assumed "safe" working pressures from 22 lb. to 18 lb., and allowed shifts of eight hours or more; and exposures of this length have been used on this contract. A bends incidence, over the whole undertaking, of less than 2% has been regarded as satisfactory by the Institution of Civil Engineers. Reports of undertakings comparable with that discussed here are somewhat scanty. During the construction of a caisson (Lewis and Paton, 1957) an overall incidence of 4% was recorded. At the Tyne Tunnel (Paton and Walder, 1954) for pressures over 18 p.s.i. it was 0·87%, with three cases of paraplegia. In the Dartford pilot tunnel built in 1937-8, the overall incidence was 0·9%. It is satisfactory, therefore, that despite the large number of compressions (119,000) at a pressure of over 16 p.s.i. and up to 28 p.s.i. there has been no fatal case, no permanent disability and an overall incidence of 0·55% (over 18 p.s.i. 0·93%). The presence of a full-time doctor on the site (an unusual feature in such contracts) has ensured that all serious cases were properly treated. It may also have inspired a willingness by the men to return for treatment even in mild cases of bends, thus raising the recorded bends incidence.

Despite this satisfactory record, the occurrence of 650 cases of bends underlines the extent of the failure to abolish the disease. In planning a further attack on the problem of reducing the incidence of bends the first requirement is as full an account as possible of the natural history of the condition. For this reason alone, the confirmation that a process of acclimatization exists, and the further discovery that acclimatization is lost in a week or two if work under pressure ceases, is valuable; for without this knowledge it would be nearly impossible to reach a correct interpretation of the success or otherwise of particular decompression procedures. The cause of acclimatization and its loss remains obscure; it might be that the nuclei available for bubble-formation become used up (Harvey, 1951); or that the nerve endings responding to the painful stimulus produced in "bends" become adapted. The suggestion advanced by Paton and Walder (1954), that it followed an acclimatization to muscular exercise in general cannot be held, now that we know that work at a lower pressure does not acclimatize to work at a higher pressure. If acclimatization could be deliberately induced, without harm, and retained, this alone could lower the bends rate by a large factor; but no means of doing this can yet be indicated.

An obvious possibility for lessening the incidence of the disease is the elimination of susceptible subjects. Unfortunately at present there exists no means of identifying such men, save by seeing whether they get bends. Once employed, they are often willing to continue employment, with its high rates of pay, despite continuing occasional attacks. Our observations on lung pathology suggest that further investigations should be made into the possible relationship between the susceptibility to decompression sickness and lung lesions of a kind hitherto disregarded. This is being attempted.

A further scope for improvement is by modification of the decompression procedures. This has the troublesome feature that any improvement so far envisaged will lengthen the time the men are on the site, without increasing their useful working time. It is quite clear that two assumptions of current decompression theory, *viz.*, that work in compressed air below 18 p.s.i. is absolutely safe, and that a man is fully saturated with nitrogen at four hours, are wrong. The question in this context simply becomes that of balancing an acceptable incidence of bends against a tolerable decompression time. There is lacking, however, any knowledge of what the incidence would be for an assumed safe pressure of 15 p.s.i., and full saturation time of eight hours; to know this would greatly assist the balancing of the issues. A further complication arises where bends follows some sort of injury; it may be that the site of an injury would give rise to pain on decompression at much lower pressures than normal.

Even if minor bends cannot be eliminated in the immediate future, the prospect seems more hopeful as regards the more important serious cases. The two cases we have described, who proved to have cysts in the lungs, exhibited a sequence of events which has occurred in serious cases elsewhere. Further, the character of these attacks and their

severity are such that it is difficult to believe that the mechanism of their production is similar to the harmless limb pains of bends. A large potentially valvular airspace, however, could account for massive air embolism under changing pressure and we suspect that a good many other serious cases may have been due to a mechanism of this type. Routine chest radiographs should serve to eliminate men with such lung cysts from the population at risk (unless the cyst actually arises during a decompression).

The treatment of decompression sickness has also been studied. Two general approaches may be made to the problem; in the first (as in the U.S. Schedule for therapeutic recompression), one may choose high pressures in the hope of compressing any bubbles present and securing their rapid solution; the second approach is to keep the therapeutic pressure as low as possible, so as to minimize any contribution which absorption of nitrogen during the recompression itself may make to recurrence of the lesion. On the whole our experience has supported the second approach; the need for subsequent recompression has been least when compression to the lowest effective pressure was used.

We are most indebted to Mr. J. Kell of Mott, Hay & Anderson, and to Mr. R. H. Falkiner of Messrs. Edmund Nuttall, Sons & Co. Ltd., and to Mr. E. Ll. Earp, O.B.E., contractor's agent, for their helpful cooperation; to the Air Ministry for the loan of the radiographic apparatus; and to Dr. R. C. Norton of the M.R.C. Head Office, for discussion and advice.

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Brit. J. industr. Med., 1960, **17**, 181.

A COMPARISON OF THE "HIGH-ALTITUDE" AND "HIGH-PRESSURE" SYNDROMES OF DECOMPRESSION SICKNESS

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(RECEIVED FOR PUBLICATION NOVEMBER 17, 1959)

Decompression sickness is an illness which occurs in divers and caisson workers on return to normal atmospheric pressure after working at very high pressures, and in airmen on reaching very low pressures at great altitude. The disease seen after exposure to high pressure is described and compared with that seen on exposure to great altitude. Mild cases show little difference, but serious ones vary sufficiently to justify division of the disease into two distinct syndromes, high-pressure and high-altitude decompression sickness.

Both syndromes are caused by the formation of gas bubbles in the blood and body fluids when the tension of dissolved gases becomes sufficiently greater than that of the surrounding atmosphere. These bubbles are composed of a mixture of gases, but their formation is determined mainly by the degree of supersaturation with nitrogen. The diver must first absorb excess nitrogen on exposure to pressure, and it is the subsequent release of this excess on return to the surface which causes decompression sickness; since his stay at pressure is limited, bubbles arise mainly from tissues which can absorb the excess gas readily. In the airman, on the other hand, all tissues are completely saturated with nitrogen before he is exposed to low pressure, and bubbles may arise equally well from any tissue. Nitrogen is much more soluble in fat than in water, so that fatty tissues can form a large reservoir of dissolved nitrogen which may later form a source of bubbles; but the blood supply of fat is poor and nitrogen diffuses slowly through it, hence although the potential capacity of the fatty tissues for excess nitrogen is great, they can only absorb it slowly. Obesity is therefore a major hazard in high-altitude decompression sickness, but relatively unimportant in the high-pressure syndrome. Liability to the airman's sickness increases markedly with age, but the incidence of the diver's syndrome is affected both much less and later in life.

Decompression also involves great changes in the working atmosphere, and the effects of these and their possible influence on decompression sickness are discussed.

High-pressure Decompression Sickness (Divers' Bends and Caisson Disease)

According to Hill (1912), the condition was first described in caisson workers by Pol and Watelle (1854) and in divers by de Mericourt (1868); both authors realized that the cause was the reduction in pressure and not merely exposure to pressure. It occurs only if the pressure has been high and the decompression rate fast (Bert, 1878; Hill, 1912), and in fact, it is never seen after dives to less than 42·5 ft. (2·25 atmospheres) and it can be prevented by gradual decompression (Haldane, 1907). The most common symptom is joint pain, "bends", which occurs either during decompression or up to 14 hours afterwards (Snell, 1896); this passes off in time, varying from a few hours to nearly a week, or immediately on recompression, and is not dangerous, though it can be extremely severe. The faster the rate of decompression, the greater the frequency of "bends" and of all other symptoms. Itching, particularly of the skin of the legs, is almost as common as "bends" and equally harmless. Respiratory symptoms occur rarely, and are poorly described; the symptom known as "chokes" appears to be characterized by dyspnoea without cyanosis and a sense of oppression in the chest (Oliver, 1899), and Coleman (1904) describes them as "urgent

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attacks of dyspnoea, during which the patient felt his lungs distended, then a cough was set up, during which quantities of gas . . . issued from the mouth". Epileptiform attacks and temporary vertigo occur frequently in caisson work (Snell, 1896; Heller, Mager, and von Schrötter, 1900) but there is no permanent damage. The most serious consequence of decompression is a spastic paraplegia with paralysis of the bladder and urinary retention, and though often permanent, partial and even complete recovery is surprisingly frequent (Blick, 1909), but in the past, many succumbed eventually to renal infection or bed sores.

Aseptic necrosis of bone may occur, but symptoms do not appear until three or four months after exposure; it is fairly massive, often multiple, and usually affects the head or lower diaphysis of the femur and upper tibia, and occasionally the upper humerus (Kahlstrom, Burton, and Phemister, 1939).

Many deaths are recorded, and these fall into two groups, those dying within a few hours of decompression and those dying from the late secondary effects of paraplegia (Heller *et al.*, 1900). Many of those dying immediately showed premonitory mottling of the skin, subcutaneous emphysema, or complained of abdominal pain.

High-altitude Decompression Sickness

The first to record symptoms of decompression sickness at low pressures was von Schrötter (1906), according to Boycott and Haldane (1908). He exposed himself to an atmosphere of 230 mm. Hg (29,500 ft.) and noticed joint pains, but concluded that they could not have been due to caisson disease; Boycott and Haldane comment, however, "we think . . . he was probably mistaken, and that the risk of caisson disease at very low pressures ought to be taken into account". The first authentic case of high-altitude decompression sickness was not recognized, however, until 1938 (Boothby and Lovelace), though it rapidly became recognized as an entity with the great increase in high-altitude flying during the second world war.

The following account, based on published descriptions and personal observation, is practically confined to subjects exposed to low pressures in a partially exhausted "decompression chamber", rather than in aircraft. Under these conditions, high-altitude decompression sickness is never seen below 23,000 ft. (307 mm. Hg), and extremely rarely below 30,000 ft. (225 mm.), but it occurs increasingly frequently at greater altitudes (Gray and Masland, 1946).

The most common symptom is joint pain, apparently identical with divers' bends, also occurring most frequently in the knees, though any joint may be affected except those of the spine, ribs, sternum, and skull (Swann and Rosenthal, 1944; Gray, Mahady, Masland, and Wigodsky, 1946). Pain is felt in or around the joint, and is often localized to muscle insertions (Gray and Masland, 1946); itching of the skin is also frequent, and as in the high-pressure form, is most common in the legs; on descent both symptoms disappear completely at about 27,000 ft. Faintness occurs, but as the incidence falls off rapidly in successive exposures it is possibly partly psychological in origin (Ferris and Engel, 1951) though in some patients it precedes collapse after descent. Chest pain, known as "chokes", occurs more frequently and differs somewhat from high-pressure chokes; it consists of a substernal burning pain with a deep-seated nonproductive cough, both of which are aggravated by deep respiration, and dyspnoea with a feeling of suffocation and apprehension (Gray *et al.*, 1946). Patchy erythema and cyanosis, and localized emphysema of the skin also occur occasionally, as in the high-pressure form, and frequently presage collapse.

The neurological symptoms are quite different from those of high-pressure decompression sickness; paralysis is extremely rare, and when it does occur, it is found at least as commonly in the arm as in the leg. The first recognized case of high-altitude decompression sickness (Boothby and Lovelace, 1938) presented as a temporary paraplegia, but in the millions of real and simulated high-altitude flights made since, only four further instances have been described; two of these were evanescent (Masland, 1943; Benzinger, 1950), and only two showed a persistent paraplegia in any way resembling the lesion typical of high-pressure decompression casualties (Royal Air Force, 1950; von Döbeln and Höök, 1954). The only common symptom is homonymous scintillating scotomata, and these, like chokes, may persist for up to an hour after recompression but are never permanent.

The most serious manifestation is post-decompression shock, which, although very rare, may be fatal. Clinical evidence of shock nearly always appears after recompression is complete, and may be delayed for as long as eight hours. Subjects leave the chamber, usually having had some other symptom, but more or less fit; later they feel faint and ill, are often nauseated, frequently vomit, and are found to have a cold, clammy, cyanosed skin, shallow rapid respiration, feeble pulse, and low systolic and pulse pressures; the haematocrit is raised, and there is oliguria (Goggio and Houck, 1945; Masland, 1948; Adler, 1950; Haymaker and Davison, 1950; Sproull, 1951; Cotes, 1953;

Halbouty and Long, 1953; Haymaker, Johnston, and Downey, 1956).

In one million man-exposures to 30,000 ft. and above there were about 150 serious cases of post-decompression shock (0·015%), of which seven were fatal (Adler, 1950). With a slightly more severe mean exposure, Roxburgh (1951) found nine severe cases of collapse, including two deaths, in 20,000 decompressions (0·045%), and of these nine patients, only one was less than 27 years old. In a further series of 61 decompressions with an average age about 10 years more than in the first two, the serious collapse rate rose to 6·5% (four cases), of which one was fatal (Roxburgh, 1951).

Pathology of Fatal Cases of Decompression Sickness

The main necropsy findings in high-altitude post-decompression shock have been pleural and pericardial effusions, oedema of the lungs, acute dilatation of the heart, congestion and oedema of the brain, and a fatty liver (Goggio and Houck, 1945; Adler, 1950; Haymaker and Davison, 1950; Roxburgh, 1951; Haymaker *et al.*, 1956). In the brain, the white matter is mainly affected, showing petechiae, and perivascular oedema progressing to demyelination; in the gray matter, ischaemic changes may occur at the bases of the sulci. In the cord, the main finding is perivascular oedema and swelling of nerve fibres in the gray matter (Haymaker and Johnston, 1955). In all the cases in which it has been sought fat embolism has been found, but the emboli are never numerous, and were thought to be probably of no clinical significance (Haymaker and Davison, 1950; Haymaker and Johnston, 1955).

A syndrome corresponding to post-decompression shock probably occurs in high-pressure decompression sickness (Haymaker, 1957) and a case was described by Rudge (1907). Deaths occurring immediately after decompression from high pressures are in general poorly described and necropsy reports are inadequate, but death appears to have occurred in one of two ways: in the first it was sudden, gas bubbles were found freely in the heart and great vessels, and the cause was probably massive air embolism (Boycott, Damant, and Haldane, 1908); Hill, 1912; Haymaker and Johnston, 1955; Sillery, 1958); in the other, death occurred in coma between 15 hours and four days after decompression, and the main necropsy finding was visceral congestion, bubbles being rarely seen (Keays, 1909). This last condition may be analogous to high-altitude post-decompression shock, but the occurrence of shock after exposure to pressure has been very much less emphasized than it has after exposure to altitude.

There are few descriptions of necropsy changes in the brain in high-pressure decompression sickness, and these usually mention petechiae or larger haemorrhages (Blick, 1909), but in one case, white matter changes were found similar to those in high-altitude decompression sickness (Haymaker and Johnston, 1955). The cord changes, unlike those in high-altitude deaths, are more prominent than those in the brain, affect the white, rather than the gray matter, and comprise petechiae, frank haemorrhage, and oedema (Blick, 1909; Haymaker and Johnston, 1955). Fat embolism in fatal cases of high-pressure decompression sickness has been recorded only twice; the first case, one of caisson disease (Muir, 1941) had large and widespread emboli (Lendrum, 1958), which may well have contributed to death, and similar findings have more recently been recorded in a diver (Haymaker and Johnston, 1955).

Mild cases of the two syndromes are very similar, but severe cases differ significantly. Persistent paraplegia, aseptic bone necrosis, and death due to gross air embolism are characteristics of high-pressure decompression sickness, whereas post-decompression shock is very much commoner after exposure to altitude. Degenerative changes in the central nervous system occur in both syndromes, but are found mainly in the gray matter of the cord after exposure to pressure, and in the white matter of the brain in high-altitude decompression sickness.

An Aetiological Comparison of the Two Forms of Decompression Sickness

The cause of both syndromes is intimately associated with the formation of gas bubbles in the blood and tissues on decompression. The factors governing the formation of these bubbles are, however, different in the two conditions, for the diver is first compressed, and then returns to a normal state of decompression, whereas the airman is first decompressed, returning, on descent, to a normal state of compression.

Tissue Nitrogen Saturation, Obesity, and Age

Though nitrogen forms only part of the content of these bubbles, it is the most important factor in both their initiation and maintenance (Haymaker, 1957). As the diver descends, excess nitrogen dissolves in the tissues, but he must be exposed to nitrogen under pressure for a definite time in order to absorb sufficient gas to form bubbles on decompression. The rate at which tissues take up excess

gas depends mainly on their blood supply, and the total mass they can absorb, on its solubility in the tissue substance. Nitrogen is five times more soluble in fat than in water (Vernon, 1907), and the tissues may be divided into the fatty and the watery, according to their affinity for nitrogen. Watery tissues have a low storage capacity for nitrogen, and usually a good blood supply, and are therefore easily saturated. Fatty tissues, on the other hand, have a large nitrogen storage capacity, but a poor blood supply, and are saturated only with difficulty, particularly since the diffusion rate of nitrogen through fat is slow (Campbell and Hill, 1933a). Fatty tissues are thus approximately synonymous with "slowly saturating tissues" and watery tissues with "rapidly saturating" ones.

In man, the time taken to reach a mean body saturation of even 94% was estimated to be about five hours (Boycott *et al.*, 1908) but "in parts of the body that are the seat of bends, a still slower rate of saturation may exist", and Campbell and Hill (1933a and b) produced evidence that the rates of saturation found experimentally were, in fact, considerably slower than this. Caisson workers usually work four-hour shifts, and divers spend up to half an hour on the bottom, but in deep dives perhaps only 10 minutes. Thus caisson workers are rarely fully saturated at the end of a shift, and divers do not approach full saturation when they start decompression. Hence in high-pressure decompression sickness there is less danger of bubbles arising from the slowly saturating tissues, whereas since the airman is completely saturated before decompression they may form in any tissue.

The exact way in which bubbles form in the body is still not certain. There is little doubt that bubble formation in both types of decompression sickness depends on the tissue fluids becoming supersaturated with nitrogen, and that the degree is determined by the relative pressure drop, not by the total mass of gas held in solution; in fact in both syndromes bubbles can be demonstrated only after the pressure has fallen by a factor of about 2·25 (Haymaker, 1957).

The diver differs from the airman in two respects: first, the relative pressure drops experienced are very much greater, and secondly his slowly saturating tissues are by no means fully saturated when decompression starts. Bubble formation appears to be due to excessive supersaturation, the main sources of which are the more rapidly saturating watery tissues.

The same factors govern both saturation and desaturation so that watery tissues in the high-altitude syndrome desaturate quickly, part of their nitrogen load being shed even during ascent, but the nitrogen tension of the fatty tissues remains much higher than that of the blood throughout their long desaturation time. Hence the danger in the airman arises largely from the slowly saturating tissues, though the relative pressure drop is comparatively small.

This conclusion differs from that of Boycott *et al.* (1908), Hill (1912), and Haldane and Priestly (1935), who all considered the slowly saturating tissues to be the main cause of trouble in high-pressure decompression sickness. This would be the case only if exposure to high pressure were long enough to allow full saturation, but this is not so in practice. Obesity should then be more important in determining susceptibility to high-altitude than to high-pressure decompression sickness; although Boycott and Damant (1908) showed that fatness considerably increased the susceptibility of rats and guinea-pigs to high-pressure decompression death, this was only after complete saturation. Smith (1899) had the impression that in caisson work "heavy" individuals were more susceptible than "spare" ones, but Paton and Walder (1954) were unable to find any correlation between weight and susceptibility, and suggest that "too much importance may be attached to excessive weight in this connexion". In high-altitude decompression sickness, on the other hand, Motley, Chinn, and Odell (1945), Gray (1951), and Cotes and Gronow (1952) showed unequivocally that susceptibility increased markedly with obesity, independently of age.

Both respiratory exchange and circulation are said to decline in middle age (Boycott and Damant, 1908; Cournand, Riley, Breed, Baldwin, and Richards, 1945; Bateman, 1951), and since both would retard the processes of nitrogen exchange, one would expect an increase in susceptibility to high-altitude decompression sickness with increasing age. In fact, there is a dramatic increase in the incidence of high-altitude post-decompression collapse in the 30-40 age group compared with the 20-30 age group (Gray, 1951; Roxburgh, 1951; Cotes and Gronow, 1952). On the other hand, in high-pressure decompression sickness, the rate of nitrogen saturation would be reduced to the same degree as that of desaturation, and such an increase would not be expected. Though there is a general impression that liability to high-pressure decompression sickness does increase with age, the evidence provided both by Snell (1896) and Hill (1912) is inconclusive, and Paton and Walder (1954) found that in caissoniers working six- to eight-hour shifts the incidence of bends did not rise until after the age of 40 and rose steeply only after 50.

The Inevitable Concomitants

Exposure to either high or low pressure necessarily introduces other factors, and these inevitable concomitants are quite different in the two forms of decompression sickness.

In high-pressure decompression sickness, an increase of pressure involves an increase in the partial pressure of all the gases in the atmosphere, which may cause severally, carbon dioxide poisoning, nitrogen narcosis, and oxygen poisoning. Carbon dioxide poisoning was a common complication of diving until Haldane (1907) pointed out the cause and remedy. Nitrogen narcosis (Bean, 1945) has never been clearly distinguished from carbon dioxide poisoning; disorientation, elation, irresponsibility, and loss of consciousness with convulsions occur, and Bean suggested that excessive dilution of a gas mixture with large numbers of heavy, relatively immobile nitrogen molecules causes physical reduction of carbon dioxide diffusion, so that the tissues fail to clear it adequately and become poisoned. This idea is confirmed by the fact that argon, the effects of which can only be physical, has a similar and greater effect than nitrogen, corresponding with its greater density. Oxygen poisoning, which was first recognized by Paul Bert (1878), causes convulsions, congestion, and oedema of the lungs, with inflammatory changes in the alveoli. At three atmospheres of oxygen, sufficient is carried in physical solution in the plasma to satisfy all the metabolic needs of the body (Bean, 1945), and above this pressure its tension in the tissues is sufficient to inhibit the function of enzymes with -SH side chains and metallic prosthetic groups. Lastly divers, though not caissoniers, are bound to work in a cold atmosphere, except in tropical waters, and cold is said to cause an increase in both types of decompression sickness (Cook, 1951).

The greatest hazard at altitude is lack of oxygen. When breathing air signs of cerebral anoxia appear at 10,000-12,000 ft. (523-485 mm. Hg), with loss of consciousness at about 20,000 ft. (350 mm.); breathing oxygen at 30,000 ft. (225 mm.) is equivalent to breathing air at ground level, and at 38,000-40,000 ft. (155-141 mm.) it is equivalent to air at 10,000-12,000 ft.; the alveolar oxygen tension is therefore less than normal, even when breathing pure oxygen, at all altitudes greater than 33,000 ft. Little is known of the effect of the anoxia itself on the decompression sickness syndrome, but though Jones (1951) suggested that the increased respiratory exchange and cardiac output, due to mild anoxia, should increase nitrogen elimination and lower the incidence of the syndrome, most workers are subjectively convinced that oxygen lack increases either its incidence, its severity, or both.

High-altitude decompression is also complicated by expansion of gas in closed cavities, particularly the gut, causing discomfort or even severe colic, and also in the middle ear and nasal sinuses if the ostia are obstructed.

No account is taken of these inevitable concomitants in practically any of the work done on decompression sickness in either man or animals, but they may not be quite so unimportant as is usually assumed, and their neglect cannot easily be justified.

Conclusion

Decompression sickness is essentially a single entity, but the diver's syndrome and the airman's differ significantly. Clinically, sequelae are seen after high-pressure decompression sickness, shock after the high-altitude syndrome; pathologically, air embolism is seen only after exposure to pressure, and lesions of the central nervous system, though found in both syndromes, occur in different places in each. Aetiologically, the mass of bubbles originates in the watery tissues in the high-pressure syndrome, but in the fatty tissues on exposure to altitude. Lastly, simple pressure changes are inevitably accompanied by other environmental changes, quite different in the two conditions, and likely to have distinct physiological effects, but though they almost certainly influence the development of each syndrome, extremely little is known of their actions, and their importance has previously been overlooked.

I would like to thank Air Commodore W. K. Stewart, C.B.E., A.F.C., and Professor F. G. Young, F.R.S., for much help and encouragement.

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Brit. J. industr. Med., 1960, **17**, 187.

PHOSGENE POISONING CAUSED BY THE USE OF CHEMICAL PAINT REMOVERS CONTAINING METHYLENE CHLORIDE IN ILL-VENTILATED ROOMS HEATED BY KEROSENE STOVES

BY

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(RECEIVED FOR PUBLICATION JANUARY 8, 1960)

Two cases resembling poisoning by phosgene following the use of a paint remover containing methylene chloride in ill-ventilated rooms heated by an oil stove are described. Experiments carried out under similar conditions demonstrated the production of phosgene in toxic concentrations. The potential hazards from non-inflammable solvents are discussed.

The use of chemical paint removers (CPR) is increasing and it seems likely that they may be used more extensively in the home by "Do-it-yourself" enthusiasts. The widely used non-inflammable types contain chlorinated hydrocarbons as the main solvent of which methylene chloride CH_2Cl_2 is probably the most common. The toxic hazards from the vapour of the solvents themselves appear not to be great as few cases of poisoning have been reported (Schütz, 1936). However, another potential hazard, namely the production of phosgene has been drawn to our attention by two cases of poisoning, one of which was fatal. Experiments were carried out to check that the formation of phosgene can in fact take place under these conditions.

Case Histories

Case 1.—A 52-year-old painter removed the paint from the woodwork in a small room on a winter morning by applying a non-inflammable chemical paint remover. It was very cold and he kept the windows closed and used a portable kerosene stove to heat the room. The stove was not connected to a chimney. Soon after starting work he felt uncomfortable, noticing, as he stated afterwards, a burning sensation in his throat. Nevertheless he went on with the job which he finished at noon. On his way home he became aware of a feeling of tightness in the chest. After lunch an increased feeling of oppression made him call his physician. Auscultation revealed râles widespread over both lung fields and a diagnosis was made of influenzal bronchiolitis. At 6 p.m. the physician was again called. He found the patient extremely dyspnoeic and cyanotic and referred him to hospital. A few hours after arrival there the man died notwithstanding every therapeutic effort. The diagnosis was influenzal pneumonia, oedema of the lungs, and cardiac decompensation. The necropsy seemed to confirm this diagnosis as extensive degenerative changes were found in the epithelium of the trachea, bronchi and bronchioli together with haemorrhagic oedematous focal pneumonia. Bacteriological and virological investigations were not performed.

Case 2.—A 38-year-old woman in the seventh month of pregnancy treated a cupboard with a non-inflammable CPR one afternoon. The work was performed in a cellar and took about three hours. The cellar was heated by a portable kerosene stove. In the course of the evening she noted an increasing feeling of tightness in the chest; once or twice she expectorated some blood-stained sputum. A physician did not consider the symptoms alarming and prescribed a sedative. Next morning, after an uncomfortable night, she felt much worse and called the physician again. The symptoms were dyspnoea and cyanosis; the pulse rate was 120, the temperature 101°F. The doctor sent her at once to hospital where a chest radiograph showed diffuse opacities similar to those seen in cases of pulmonary oedema. Therapy included oxygen, antibiotics, and cortisone. The patient recovered and was discharged after eight days, though not all radiographic abnormalities had disappeared. Two months later she gave birth to a healthy child.

Experimental

The CPR used by Case 1 was found to contain 92% of volatile solvent consisting almost entirely of methylene chloride with small amounts of ethanol and trichloroethylene.

In each test a painted surface (wood) of 0·3 square metres was treated with approximately 50 g. of a CPR having the same composition as the one used by the deceased. Immediately after treatment the object was placed in a large cupboard 6 m.³. In the cupboard the kerosene stove used in the actual case was kept burning during each test. The door of the cupboard was kept tightly closed during each test and samples of the air were drawn from inside through a glass tube which had been inserted through a hole in the door at a height of 1·3 m. As the speed of decomposition and the relative amounts of the decomposition products formed may vary within wide limits (depending on the chlorinated hydrocarbon present and the circumstances under which the decomposition takes place (Little, 1955; Nuckolls, 1933)), we have tried to simulate the actual circumstances as closely as possible in our tests.

Methods of Analysis

In our investigation we used two different methods, one was developed by the British Department of Scientific and Industrial Research (1939) and the other by collaborators of the US Bureau of Mines and the US National Board of Fire Underwriters (Matuszak, 1934). Both methods were only slightly modified.

Method 1.—The only difference from the D.S.I.R. method consisted of the use of a centrifugal air pump with a constant rate of 1 l./min. instead of the handpump. The sampling time varied from ¼ to several minutes. The colour of the test paper was then compared with the standards and the phosgene concentration calculated.

Method 2.—100 ml. of an aqueous 0·5 N solution of KOH contained in a spiral gas bubbler was used as the absorbing medium. Air was drawn through at a rate of 0·2-0·5 l./min. for 20 min. The contents of the bubbler were then neutralized with nitric acid and the chloride content was determined using Mohr's method.

In both methods a tube containing pumice granules impregnated with a solution of potassium iodide and sodium thiosulphate was used to remove HCl and Cl_2. The efficiency of the pumice granules was first tested by drawing through the tube a mixture of HCl and Cl_2 in air. This mixture was prepared by passing the air through a series of three bubblers containing HCl(S.G. 1·09), concentrated sodium hypochlorite solution and HCl (S. G. 1·09). The air leaving the tube containing the pumice granules was then analysed as in method 2. No chloride was found.

The methylene chloride itself is not retained by the impregnated pumice granules and it leaves the tube unaltered. This will not interfere with method 1. In method 2, however, some interference might be expected (Matuszak, 1934).

This was checked by passing 30 l. of air containing 50 g. of methylene chloride per m.³ through the bubbler used in method 2. The apparent phosgene concentration found at this extremely high concentration was negligible (+5 mg./m.³) as compared with the amounts of phosgene actually found.

Finally, the methylene chloride concentration in the cupboard was determined under the same test conditions as described above, without however, burning the kerosene stove. The temperature inside the cupboard must have been considerably lower, resulting in a lower evaporation rate of the solvent. In this test methylene chloride was determined by total decomposition in a quartz tube using platinum as a catalyst at 900°C. as described by Jacobs (1949).

Results

The quantities of phosgene in the air of the cupboards determined by Method 1 are given in the Table.

TABLE

CONCENTRATION OF PHOSGENE IN A CUPBOARD IN WHICH A KEROSENE STOVE WAS BURNING, ESTIMATED AT DIFFERENT TIMES AFTER EXPOSING A WOODEN SURFACE TO WHICH A CHEMICAL PAINT REMOVER CONTAINING METHYLENE CHLORIDE HAD BEEN APPLIED.

Time after start (min.)	Phosgene	
	mg./m.³	p.p.m.
Experiment 1. (51·5 g. CPR applied.)		
11	140	32
19	200	45
26	300	68
54	55	12
Experiment 2. (54·3 g. CPR applied.)		
3	70	16
6	140	32
9	200	45
12	560	128
26	335	77
37	150	34
42	130	30
67	35	8

In two other experiments phosgene (estimated by Method 2) and methylene chloride were determined during a continuous period from the start of the experiment in which about 50 g. of CPR were applied. The concentrations of phosgene were 750 and 760 mg./m.³ in two experiments and methylene chloride 700 and 1,300 mg./m.³ in two other tests.

Discussion

The experiments which we conducted show clearly that methylene chloride is decomposed at a high rate—phosgene being the main decomposition product—when the vapours are present in a closed cupboard in which a portable kerosene stove is burning. This is rather surprising as other investigations have shown that in different circumstances (decomposition by hot surfaces) the decomposition rate of methylene chloride is very low, much lower

in fact than that of other chlorinated hydrocarbons. Moreover, the production of phosgene has always been found to be low in comparison with the production of hydrogen chloride, and chlorine (Little, 1955; Nuckolls, 1933).

The findings of our experiments may possibly be explained by the fact that the methylene chloride vapour is mixed with the air used for the combustion of kerosene in the stove. The vapour thus passes through the flames, coming into close contact with carbon monoxide at high temperatures. Any chlorine formed by decomposition may under these conditions react with carbon monoxide and form phosgene. Indeed the passing of chlorine together with carbon monoxide over carbon black actually is one of the processes by which phosgene is produced (Ullmann, 1929). Moreover the combustion products of the stove could not escape from the room and were being constantly recirculated, thus gradually increasing the amount of decomposition products present. Of course, our testing conditions were severe as we used a closed cupboard of only 6m.^{3} capacity. Under these conditions lethal phosgene concentrations were formed within five to 10 minutes.

Our case histories indicate, however, that under conditions such as may be encountered in practice in small, ill-ventilated rooms, lethal or dangerous phosgene concentrations can be formed within a period as short as three hours.

Preventive Measures.—As the use of non-inflammable CPR under the above-mentioned conditions constitutes a real danger, preventive measures are of the utmost importance.

Combustion stoves which do not have a proper connexion to a chimney should never be used in rooms where the CPR is being employed. With an electric stove the danger seems to be much less, but even then small amounts of phosgene may be formed together with the other decomposition products of the solvents. Heating by electric stoves therefore appears to be safe only when the room is well ventilated. In any case adequate ventilation is always necessary when using CPR in small rooms as the solvent vapours are in themselves toxic.

One aspect which constitutes a difficulty in promoting the safe use of non-inflammable CPR may finally be mentioned. It lies in the fact that the indication "non-inflammable" which is often printed on the label of the container suggests that its contents can safely be used in the vicinity of an open fire or hot surface. As this is one of the principal reasons why people select the non-inflammable CPR it will not be easy to persuade the manufacturers to qualify this statement on the label.

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Brit. J. industr. Med., 1960, **17**, 190.

A STUDY ON THE ACUTE TOXICITY OF THE TRI-ARYL PHOSPHATES USED AS PLASTICIZERS

BY

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(RECEIVED FOR PUBLICATION AUGUST 29, 1959)

Paralysis in man and the domestic fowl caused by "ToCP" (tri-cresyl phosphate, tri-tolyl phosphate or TTP) is reviewed, and the search for a non-toxic plasticizer derived either from TTP or tri-xylenyl phosphate (tri-dimethylphenyl phosphate or TXP) is described. It had been previously shown that the *ortho*-tolyl esters are toxic but we found that their removal does not make the mixture non-toxic. The *meta*- and *para*-tolyl esters were known to be free from toxic effects and the 2 : 4 and 2 : 5 dimethylphenyl esters were equally shown to be non-toxic except in massive doses. We confirmed that the tri-*ortho*-ethylphenyl ester was non-toxic, but found the mono- and di-*ortho*-ethylphenyl phosphates to be highly toxic. We showed that TTP made from phenols with all the *ortho*-cresol and *ortho*-ethylphenol removed is non-toxic.

With TXP, however, elimination of all *ortho*-cresol and *ortho*-ethylphenol from the raw materials does not result in a non-toxic plasticizer. Tri-*ortho*-*n*-propylphenyl phosphate was shown to be non-toxic but esters containing one or two *ortho*-propylphenyl groups are toxic.

The toxicity of the *ortho*-tolyl, *ortho*-ethylphenyl and *ortho*-propylphenyl groups is much reduced in the presence of the 3 : 5-dimethylphenyl group. This influence is greatest in mono-*ortho*-propylphenyl-di-3 : 5-dimethylphenyl phosphate which is non-toxic in five consecutive daily doses of 500 mg./kg. body weight.

The removal of all *ortho*-cresol, *ortho*-ethylphenol and *ortho*-propylphenol from the raw material results in a non-toxic product which we termed non-toxic plasticizer "NTP". This has been fed in various doses to a variety of mammals and a large number of chickens in short term tests without toxic effects.

Our experiments showed that tri-*meta*-ethylphenyl phosphate is non-toxic but tri-*para*-ethylphenyl phosphate is highly toxic. The mixture from which NTP is made contains 10% of *para*-ethylphenol. Based on chemical statistics the tri-*para*-ethylphenyl ester can be present only in minute quantities, and we have shown that esters containing one or two *para*-ethylphenyl groups are non-toxic. An ester with a methyl group in the *ortho*, and an ethyl group in the *para* position in the same benzene nucleus (tri-2-methyl-4-ethylphenyl phosphate) we showed, surprisingly, to be non-toxic.

Two aryl phosphate plasticizers are available commercially: tri-tolyl phosphate (TTP) which was formerly known as tri-cresyl phosphate (TCP), and tri-xylenyl phosphate (TXP). They are widely used because of their technical advantages. A plasticizer as well as making a substance more pliable may confer other desirable properties, for example, flame, abrasion and water resistance, and hardness. Unfortunately both TTP and TXP are too toxic to be used in connexion with the packaging of food; nor, since they are readily absorbed through the intact skin (Hodge and Sterner, 1943), can they be used for materials in contact with the human body.

The technical advantages of phosphate plasticizers made it worthwhile to aim at preparing one free from toxic effects. In the course of our investigations new light has been thrown on the complicated story of the toxicity of aryl phosphate esters which it is the purpose of this paper to describe.

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Phosphate Plasticizers

Tri-*ortho*-tolyl Phosphate (Tri-*ortho*-methylphenyl Phosphate).—Susser and Stein (1957) have reviewed in the literature the history of nine outbreaks of "T*o*CP" poisoning, including their own series. By far the largest outbreak was that in the U.S.A. in 1930 when 15,000 persons were affected by the adulteration of an alcoholic drink called Jamaica Ginger or Jake by 2% "T*o*CP". Most outbreaks have occurred by mixed esters being added intentionally or otherwise to food, and as abortifacients. Hunter, Perry, and Evans (1944) described three cases of industrial poisoning in England in 1942. A recent outbreak affecting 10,000 persons in Morocco was investigated by Smith and Spalding (1959).

In man the illness may start with early transient and indefinite gastro-intestinal symptoms with nausea, vomiting and diarrhoea. After about 10 days, aching and tenderness of the lower leg muscles and numbness of the toes develop, followed by paraesthesiae and loss of superficial sensation of stocking-and-glove distribution. The disturbance of sensation decreases after a few days and weakness supervenes with foot drop. Later the hands are usually affected. The victims can be identified by their high stepping gait (Smith and Spalding, 1959). The paralysis rarely extends beyond knee and elbow, and the effect passes off in the reverse order; the hands may recover completely but permanent foot drop may remain. Whilst the mortality is very low (only 10 persons in 15,000 were reported to have died in the outbreak in the U.S.A.), the paralysis is often permanent. Zeligs (1938) found that in a group of over 300 persons approximately a fifth were still in institutions six years later. In these cases the flaccid paralysis had changed to a spastic type with adductor spasm, paralytic talipes, exaggerated tendon reflexes and extensor plantar responses.

Smith, Elvove, and Frazier (1930) found that the symptom complex of ginger paralysis could be reproduced in some species of laboratory animals by the administration of the phosphoric ester of *ortho*-cresol. The symptom complex was characterized for the most part by bilateral and symmetrical flaccid paralysis of the distal muscles of the lower, and to a lesser extent of the upper, extremities with little or no sensory disturbance. Smith, Elvove, Valaer, Frazier, and Mallory (1930) in a previous report drew attention to the insensitivity of the dog and the monkey to this poison. This was later explained by incomplete absorption, but even when administered parenterally the same symptom complex was not reproduced in the monkey.

The rat is also highly resistant and oral and subcutaneous doses of up to 30,000 mg./kg. body weight in two doses of 15 g. each had no effect; but intravenously the LD_{50} lies between 500 and 1,000 mg./kg. body weight (Smith *et al.*, 1930). These authors showed that the chicken is the most useful experimental animal as it is very sensitive to the aryl phosphates and suffers effects very similar to those in man. Whether administered in doses just sufficient to produce paralysis or as much as 10 times the minimum paralysing dose the result is nearly the same, except for a difference in degree. For eight to 15 days after administration the animal is healthy but after an interval which rarely extends to 30 days the bird becomes ataxic and unsteady. Within a few days the bird cannot get off its haunches, may fall over and paralysis of the wings begins. With small doses the paralysis is partial and full or partial recovery may occur in two to three months. With larger doses the paralysis extends and after some weeks dyspnoea supervenes. This may last for days or weeks until the animal finally dies. The intravenous minimal paralysing dose is not greatly different from the oral, showing that the chicken absorbs the ester virtually completely. Nor is the latent interval altered by the route of administration. Smith, Engel, and Stohlman (1932) were also the first to show that the daily ingestion of very small, and in themselves, ineffective doses, of tri-*ortho*-tolyl phosphate over a period of days gives rise to flaccid paralysis; as little as 5 mg./kg. body weight daily produces the syndrome.

The histopathology was first described by Smith and Lillie (1931). The lesions due to tri-*ortho*-tolyl phosphate were shown to be mainly in the lumbar and cervical portions of the spinal cord. Cavanagh (1954) states that degeneration of axis cylinders and myelin sheaths is found in both the peripheral nerves and long tracts of the spinal cord, affecting the distal extremities of the axons. Long fibres of large diameter are particularly selected by T*o*CP. It was these regions which received our attention when one of us (E.J.F.) undertook the histology of animals dosed with a series of chemicals to be described in the development of a non-toxic plasticizer.

Tri-*meta*-tolyl Phosphate and tri-*para*-tolyl Phosphate.—Smith *et al.* (1930) showed that the tri-*meta*-tolyl and the tri-*para*-tolyl phosphates were non-toxic. Hunter *et al.* (1944) confirmed the lack of toxicity of the *para*-tolyl ester but found that the *meta*-tolyl, although not as toxic as the *ortho*-tolyl was still toxic: cockerels, 12 weeks old, showed weakness of the legs after receiving 12·5 g. of tri-*meta*-tolyl phosphate. Aldridge (1954), Hine, Dunlap, Rice, Coursey, Gross, and Anderson (1956) and Henschler (1958), on the other hand, have shown that if a phosphate ester is made from pure *meta*-

cresol, pure *para*-cresol or a mixture of the two, the resulting ester is non toxic. We have confirmed these results in our own series, finding both the tri-*meta*-tolyl and *para*-tolyl phosphates non-toxic to chickens, and it appears likely that Hunter's *meta*-tolyl ester must have been adulterated with one of the *ortho*-tolyl esters.

Commercial tri-tolyl Phosphate.—For many years this material has been made from a phenolic fraction containing *ortho*-, *meta*- and *para*-cresols and xylenols. This fraction is reacted with phosphorus oxychloride and a number of esters is formed which contain not only the symmetrical tri-esters but mixed esters as well. Tri-*ortho*-tolyl phosphate is one of the esters present in commercial TTP and as it was considered that the toxicity of TTP was solely dependent on the amount of *o*-cresol present in the raw material from which the esters are made, some countries demand that any cresol fraction used in the preparation of TTP should contain not more than 3% *ortho*-cresol. This provision has indeed reduced, but equally has by no means abolished, the toxicity of commercial TTP. Barnes (1958) and Henschler (1958) have shown that a mixed ester which contains either one or two *ortho*-tolyl groups in the molecule is more toxic than tri-*ortho*-tolyl phosphate itself. Henschler (1958) found that a TTP made from raw material containing 30% *ortho*-cresol is 10 times as toxic as one made from pure *ortho*-cresol, and that an ester with one *ortho*-group is much more toxic than one which contains three *ortho*-groups, with the di-*ortho* compounds intermediate in toxicity. This means that an analysis must include all the mixed esters that can be formed from the various phenols in the mixture. The fact that a tri-substituted ester could be non toxic but a mono-substituted ester with the same phenol could be toxic meant that a more detailed analysis was needed. At first sight the demonstration that tri-*o*-ethylphenyl phosphate was not toxic (see below) might have led to the assumption that *o*-ethylphenol could safely be left in the raw materials. It is important to remember that mono-substituted esters are those most likely to be formed by impurities.

An ester made from *meta*- or *para*-cresol has the same technical advantages as TTP or TXP, but the isolation and high degree of purification of the *meta*- and *para*-cresol in the first instance makes the cost commercially prohibitive. We therefore decided to attempt the purification of the commercial raw material used in the production of TTP and TXP; and, as a first step, we isolated the component phenols and tested the toxicity of their phosphate esters. This work has been in progress since 1956.

Materials and Methods

Preparation of Esters.*—The phosphate tri-esters were prepared by reacting 1 mol. of phosphorus oxychloride with 3 mol. of the phenolic material and the resulting ester was purified by fractional distillation under high vacuum. The impurities were isolated and identified.

The general method used for the preparation of the mixed esters consisted of reacting the first phenol (2 mol.) with phosphorus oxychloride (1 mol.) to give the diaryl phosphorochloridate. This material was rigorously purified by fractional distillation and its purity checked by analysis; it was then reacted with the second phenol in alkaline solution under Schotten-Baumann conditions. The resulting mixed ester was purified by distillation under very high vacuum (taking great care to avoid any disproportionation) and by recrystallization when possible.

Three groups of phosphate esters were used: (1) pure tri-esters, (2) mixed esters from two phenols of definite chemical composition and (3) phosphate esters from a mixture of phenols. Their formation and properties are given in Tables 1, 2, and 3. With regard to esters from a mixture of phenols it is not possible to give an analysis of the esters themselves, but a composition of the phenolic material is given which has been evaluated by fractional distillation and infra-red analysis. All the phosphate esters used were purified by fractional distillation under high vacuum. Solid phosphate esters were recrystallized to a constant melting point. All the mixed esters were analysed for carbon, hydrogen and phosphorus†.

Further details about the chemical preparations and their purification will be published elsewhere.

Animals.—Fowls were mainly Light Sussex X Rhode Island Red or White Leghorn X Light Sussex, of both sexes, obtained from the Houghton Poultry Research Station. For a limited number of experiments, advantage was taken of the availability of Incross chickens produced at the National Poultry Institute Northern Breeding Station, Reaseheath, Cheshire (Clough and Cock, 1957). Barnes and Denz (1953) have shown that young birds at the time of administration of di-*iso*propyl fluorophosphate (DFP) may fail to develop characteristic signs or lesions. To check this age factor preliminary experiments, each involving a group of 10 Incross chickens, showed that a single oral dose of 1,000 mg./kg. body weight of T*o*CP was without effect when administered at 10, 20, 30, 40 or 50 days of age, but neurotoxic when administered at 72 or 100 days of age. The birds dosed at up to 50 days were subsequently maintained alive for a year, but none developed symptoms. Later we took 100 days of age as a minimum in all our toxicity testing in chickens except in cases where we brought young birds up on a diet containing an aryl phosphate plasticizer so that they became accustomed to this oily solution in their food. All birds were maintained on the premises for not less

* The isolation and identification of single phenols from phenolic fractions was carried out by J. Gumb. The synthetic phenols and the phosphate esters were prepared by A. Gregory. Both are members of the Research Department of Coalite and Chemical Products Limited.

†The phosphorus analyses were done by C. R. Kennedy of the Medical Research Council's Toxicology Research Unit.

than 14 days prior to dosing, with checks on body weight and on the excretion of coccidial öocysts in the faeces. Any birds that were suspected to be ailing, or to have died from a non-specific cause, were subjected to detailed examination at the Houghton Poultry Research Station.

Administration and Dosing.—Oral dosing, except where otherwise stated, was given with the test substance in arachis oil or in an emulsion comprising arachis oil 10 parts, gum acacia 3 parts and water 10 parts, and administered by stomach tube. During the course of our toxicity testing we discovered that, while birds might be unaffected by a single dose of 2,500 mg./kg. body weight, an ester might prove toxic in five consecutive daily doses of 500 mg./kg. body weight.

Smith *et al.* (1930) had found that a single dose of 50 mg. of T*o*CP/kg. body weight, or repeated doses of 5 mg./kg. body weight, caused paralysis. We regarded 50 times the dose level proposed by Smith *et al.* (1930) (*i.e.*, five doses of 500 mg./kg. body weight) as an appropriate level at which to determine whether our aryl phosphate was toxic or not. In many tests much larger doses were given, sometimes up to 500 times Smith's dosing.

Diagnostic Procedures

Clinical Observations.—The effects of test doses were studied by clinical observation and routine weighings. After the administration of tri-tolyl phosphate, which is known to be toxic to chickens, there is a steady deterioration in weight. The earliest nervous damage noted is observed usually about the eighth or tenth day after the initial dose when the birds tend to squat unless they are disturbed. The birds have a high stepping gait of a tabetic character and are clumsy, particularly after exercise; in addition there is unsteadiness on landing after flight. Whilst standing still the hocks turn in unequally and the feet are spread widely to maintain balance.

Muscular incoordination becomes progressively worse over the next four to five days, paralysis supervenes on the ataxia, and birds sink on to their hocks whilst attempting to run. The weakness is most apparent in the legs; the wings are still capable of strong action at this stage. Unless the dosage has been heavy, recovery may start at this point. The signs of ataxia and paralysis pass off in the reverse order. With heavier doses the paralysis progresses with continuing loss of weight until the birds are helpless, with legs extended forward from the hip joint and the wings drooping, but some movement in the wings is possible until death. Birds in this stage are weakened by starvation and die from inanition.

The dosage level is of some importance in the degree of ataxia and paralysis caused; but there is a critical dose, remarkably constant at about 50 mg./kg. body weight with TTP, where some nervous damage always occurs in chickens. This critical level of dosage is also independent of its administration as one single dose, or in divided portions over days. Neurological signs are not, however, advanced by increasing the dosage.

Cholinesterase Determinations.—Plasma cholinesterase was determined with a Warburg respirometer by the method of Ammon (1933). Total and pseudo cholinesterase in brain were determined by the method of Earl and Thompson (1952) and with a Warburg respirometer.

Pathological Examination.—Animals for post-mortem examination were killed by exsanguination under anaesthesia. Material for histological examination was fixed in 10% formol. In our hands preparations fixed by perfusion showed no significant advantage for Marchi staining over those fixed by immersion so that after preliminary trials the latter method was uniformly used. The brain, after removal, was fixed for 48 hours before being sectioned. Complete laminectomy was performed to allow free access of fixative to the cord for 36 to 48 hours. Following this the cervical, thoracic, and lumbosacral portions of the cord were dissected out. The lumbosacral portion included the glycogen body. Paraffin sections of the brain at pituitary level, the medulla and at various cord levels were prepared and stained by Giemsa's stain and haematoxylin and eosin.

Pieces of cervical, thoracic, and lumbosacral cord 1-2 mm. thick, and carefully cleaned 2 cm. lengths of upper and lower sciatic nerve were impregnated by the method of Poirier, Ayotte, and Gauthier (1954), in their modification of Swank and Davenport's (1935) adaptation of the Marchi method.

Histological Findings.—The Marchi preparations occasionally showed artefacts which could be readily recognized and were present equally in dosed and undosed birds. But when a toxic material, for example tri-*ortho*-tolyl phosphate was given, demyelination was massive and most prominent in the lumbar sections of the cord, except in cases of long standing when the cervical region showed equal or even greater demyelination. The brain and spinal cord had normal nerve cells and the appearance in the sciatic nerves was variable, but some demyelination was usually present. Some birds showed many degenerated fibres with light brown myelin droplets alongside fully blackened ones.

Results

Tri-tolyl Phosphate (*o*-cresol removed from the Phenolic Fraction).—The raw material contained the phenols given in Table 1. By careful fractionation of a cresol fraction the *o*-cresol was removed (Table 1) and the remainder reacted with $POCl_3$ and the ester formed. This ester was given in two consecutive daily doses of 250 mg./kg. body weight to two chickens and both birds became ataxic. This was repeated on another six chickens which were given two daily doses of 500 mg./kg. body weight, and, of the group, five became paralysed. One of these on histological examination showed demyelination.

At this time it was considered that the raw material contained only *meta*-cresol, *para*-cresol, 2 : 4 and 2 : 5-dimethylphenol. Many workers, including ourselves, have shown that the phosphates of the *meta*- and *para*-cresols are non-toxic. One

TABLE 1

PERCENTAGE COMPOSITION OF PHENOLIC FRACTIONS USED TO MAKE PHOSPHATE ESTERS

	ortho-Cresol	2 : 6-Xylenol	*meta*-Cresol	*para*-Cresol	*ortho*-Ethylphenol	ratio 2·4 : 1 2 : 4/2 : 5-Xylenol	2 : 3-Xylenol	*ortho*-Propylphenol	2 : 4 : 6-Trimethylphenol	*meta*-Ethylphenol	*para*-Ethylphenol	3 : 5-Xylenol	ratio 2·5 : 1 2-methyl-4-ethylphenol : 2-methyl-5-ethylphenol	3 : 4-Xylenol	Mixture of phenols boiling from 228-230° C.
Melting point °C.	30·8°	49°	10°	34·4°	—	—	75°	—	69°	−4°	45°	68°	—	65°	—
Boiling point °C.	191°	201°	202·2°	202·3°	204·5°	211.5	217°	217·5°	219°	218·5°	218°	221·5°	224·5°	227°	228-230°
Commercial phenolic fraction for TTP	3	6	42	30	3	16									
Phenols free from *o*-cresol		6	43	31	3	17									
Phenols free from *o*-cresol and *o*-ethylphenol			47	34		18									
Synthetic phenol mixture			47	34		19									
Xylenol fraction as manufactured in 1955	0·5	0·5	4	3	0·5	7	10	1	3	25	20	12	6	3	4·5
Xylenol fraction free from *o*-cresol and *o*-ethylphenol since 1956 for TXP	<0·01				<0·01	5	8	1	5	22	18	17	15	5	4
Xylenol fraction free from *o*-cresol, *o*-ethylphenol and *o*-propylphenol used for NTP	<0·01				<0·01		1	<0·1	1	12	10	25	27	20	4*

*This fraction consists of a mixture of the following phenols: 2 : 6-dimethyl-4-ethylphenol, 2-methyl-3-ethylphenol, 2 : 3 : 5-trimethylphenol, *meta*-propylphenol, *para*-propylphenol.

chicken, dosed with a single dose of 2,500 mg./kg. body weight of tri-*meta*-tolyl phosphate, remained healthy in all respects and increased in weight. Three birds given similar single doses of tri-*para*-tolyl phosphate also had no signs of any kind and two of the three gained weight. From these observations we assumed that the 2 : 4 and 2 : 5-dimethylphenols must be the toxic element so we prepared tri-2 : 4, 2 : 5 dimethylphenyl phosphate free from *ortho*, *meta* and *para* tolyl and *ortho*-propylphenyl esters, which was given in five consecutive daily doses of 500 mg./kg. body weight (total 2,500 mg.) to six chickens. But the birds remained healthy in all respects. This is in agreement with other workers who have studied the tri-xylenyl phosphates. On the other hand Henschler and Bayer (1958) found that two of the six xylenyl phosphates tested produced some ataxia in very large doses (1,000 mg./kg. body weight daily for 40 days). Although we found the esters from 2 : 6, 2 : 4, 2 : 5, 2 : 3, 3 : 5 and 3 : 4-xylenols to be non-toxic when given in doses of 5 × 500 mg./kg. body weight, we repeated the work of Henschler and Bayer with tri-2 : 3-xylenyl phosphate at their dose level and found that the birds became paralysed. Nevertheless the toxicity of TTP minus the *ortho*-tolyl esters could not be accounted for by the presence of 2 : 4 and 2 : 5-dimethylphenyl esters, when given in doses of 5 × 500 mg./kg. body weight.

Tri-*ortho*-ethylphenyl Phosphate.—After the removal of *o*-cresol there remained 3% *o*-ethylphenol (Table 1). On the basis of the non-toxicity of the xylenol derivatives and the toxicity of T*o*TP it was assumed that one *ortho* group was necessary to produce toxic effects and that more than one group on the phenolic ring would prevent toxicity.

In two separate experiments using 10 chickens in each batch, birds were dosed with five consecutive daily doses of 500 mg./kg. body weight of tri-*ortho*-ethylphenyl phosphate (2,500 mg. in all). The birds were unaffected, thus confirming the lack of toxicity of tri-*ortho*-ethylphenyl phosphate found by Hine *et al.* (1956). Our first experiments with a less carefully purified material had produced some toxic effects.

We therefore prepared:

Mono-*ortho*-ethylphenyl di-*para*-tolyl Phosphate.—As the phenolic fraction from which the *ortho*-cresol was removed contains only 3% of *ortho*-ethylphenol it must be assumed that the phosphate ester will contain only minute quantities of the tri-ester. The *ortho*-ethylphenyl group will therefore be present in mixed esters, containing one or two *ortho*-ethylphenyl groups.

Earlier findings show that mixed esters, containing one or two *o*-tolyl groups are much more toxic than tri-*ortho*-tolyl phosphate and we considered that the toxicity of TTP containing no *ortho*-tolyl ester might be due to the presence of esters containing one or two *ortho*-ethylphenyl groups.

Mono-*ortho*-ethylphenyl di-*para*-tolyl phosphate was synthesized and tested for toxicity. Single doses

of 1,000 mg./kg. body weight were given to five birds. All the birds became severely paralysed. Single doses of 250 mg./kg. body weight given to three birds similarly paralysed them all. In a series of further experiments we showed that a dose of 50 mg./kg. body weight, whether given as a single dose or as 5 × 10 mg., paralysed all birds.

Di-*ortho*-ethylphenyl mono-*para*-tolyl phosphate was also found to be toxic. Three out of four chickens dosed with 5 × 500 mg./kg. body weight became paralysed. This was confirmed by Barnes (1958). Two birds dosed by him with 1 ml./kg. body weight became ataxic, whereas two others on 0·2 ml./kg. showed no effects.

We can therefore state that the toxicity of commercial TTP is due not only to the presence of phosphate esters containing one, two or three *ortho* tolyl groups but also due to the toxicity of phosphate esters containing one or two *ortho*-ethylphenyl groups.

TTP made from a raw Material (*ortho*-cresol and *ortho*-ethylphenol having been Removed).—It is obvious that we had to remove both *ortho*-ethylphenol and *ortho*-cresol from the raw material used in the production of TTP. The removal of *o*-ethylphenol is not easy because the boiling points of *ortho*-ethylphenol and *meta-para*-cresol are very close and are almost identical if distilled under a vacuum. Although it is not possible to remove the *ortho*-ethylphenol by fractionation it is more steam volatile than *meta*- and *para*-cresol and we attempted its removal by azeotropic distillation with water under vacuum; probably a small amount still remained in the raw material.

The TTP made from this raw material was then fed to two chickens in two consecutive doses of 250 mg./kg. body weight each, and six further birds were given two doses of 500 mg./kg. body weight. The birds were unaffected.

We next dosed seven birds with five consecutive doses of 500 mg./kg. body weight (2,500 mg./kg. body weight total dose). Five of the birds became paralysed and one of these was histologically examined and found to have demyelination.

Synthetic Phenol Mixture.—We prepared a mixture containing 47% *meta*-cresol, 34% *para*-cresol and 19% 2 : 4, 2 : 5-dimethylphenol from pure phenols. These appeared to be the only remaining ingredients in the original phenolic mixture. From this mixture we formed the ester. Twelve birds were given 2,500 mg./kg. body weight in five consecutive 500 mg. daily doses and were not affected. This phosphate ester is therefore non-toxic, indicating that some toxic impurity had remained in the previous preparation. The complete removal of *ortho*-cresol and *ortho*-ethylphenol from commercial TTP would be so costly that the resulting TTP would be too expensive, and we therefore turned our attention to trixylenyl phosphate (TXP).

Tri-xylenyl Phosphate.—In 1955, TXP was manufactured from a phenolic fraction (see Table 1) which contained all the xylenols, *meta*- and *para*-ethylphenol, methylethylphenols and *meta*- and *para*-cresol. This material was found to be about one fifth as toxic as TTP. In other words, doses of up to approximately 1,000 mg./kg. body weight could be given to chickens without clinical effect, but if the dose was increased beyond this, toxic effects became apparent so that it would be necessary to remove some toxic impurity.

TXP from Raw Material minus *ortho*-cresol and *ortho*-ethylphenol.—By careful fractionation in the laboratory we prepared a material free from both *ortho*-cresol and *ortho*-ethylphenol, as shown in Table 1. The phosphate ester was formed from this new raw material. Thirteen birds were given 1,250 mg./kg. body weight in two consecutive daily doses of 625 mg. No toxic effect was found and histological findings were negative. Later the dose was increased to 5 × 500 mg./kg. body weight (2,500 mg./kg. total), and four out of 12 birds showed signs of ataxia.

The raw material for the production of TXP was now free of *ortho*-cresol and *ortho*-ethylphenol and in consequence the toxicity of the TXP had been reduced to one tenth that of TTP, although we had not succeeded in making a non-toxic tri-xylenyl phosphate.

***Ortho*-propylphenol.**—On the theory that a phenolic compound having one group in the *ortho* position gives rise to toxic phosphate esters, we examined the phenolic raw materials from which TXP is produced for the presence of *ortho-n*-propylphenol. There is no indication in the literature that coal tar xylenols made from British coal contain *ortho-n*-propylphenol although it has been identified in German coal tar (Steinkopf, 1941).

We found that the xylenol fraction from which TXP is made contains 1 to 1·5% of *ortho-n*- propylphenol, hence we decided that the toxicity of phosphate esters containing *n*-propylphenol should be investigated.

Tri-*ortho-n*-propylphenyl Phosphate.—A supply of *n*-propylphenol was obtained from an outside source and tri-*ortho*-propylphenyl phosphate was prepared. No clear conclusions about the toxicity of this preparation could be drawn, because the results on chickens were not consistent. We therefore synthesized the *n*-propylphenol and carefully

TABLE 2
PHYSICAL CONSTANTS AND TOXICITY OF SYMMETRICAL TRI-ARYL PHOSPHATES

Compound	Boiling Point at 1 mm. Hg (°C.)	Refractive Index (n_D^{20})	Toxicity (Ataxia in Chickens*)
Tri-*o*-tolyl phosphate	207-209°	1·5603	+
Tri-*m*-tolyl phosphate	224-226° (m.p. 23°C.)	1·5566	—
Tri-*p*-tolyl phosphate	236·5-238·5° (m.p. 78·5°C.)	—	—
Tri-*o*-ethylphenyl phosphate	221-223°	1·5508	—
Tri-*m*-ethylphenyl phosphate	230-232°	1·5468	—
Tri-*p*-ethylphenyl phosphate	247·5-249·5°	1·5480	+
Tri-*o*-normal propylphenyl phosphate	247-249°	1·5422	—
Tri-(2-methyl-4-ethyl-phenyl) phosphate	265-267°	1·5465	—

* Ataxia with or without paralysis in chickens within 30 days of dosing with 500 mg./kg. or higher dose.

purified it. The tri-*ortho*-propylphenyl phosphate was formed and this also was purified. We gave 5 × 500 mg./kg. body weight of this compound to eight birds and all the birds remained healthy. We can, therefore, state that, like tri-*ortho*-ethylphenyl phosphate, tri-*ortho*-propylphenyl phosphate is non-toxic.

Mono - *ortho* - propylphenyl di - *para* - ethylphenyl Phosphate.—As in the case of *o*-ethylphenol, mixed esters containing one or two *ortho*-propylphenyl groups might be toxic. Our raw material contained 18% *p*-ethylphenol so we synthesized mono-*ortho*-propylphenyl di-*para*-ethylphenyl phosphate by two different methods, and both preparations were tested for toxicity. In three experiments 12 birds were each given single doses of 1,000 mg./kg. body weight and all birds were severely paralysed. Another three birds were given single doses of 500 mg./kg. body weight and all showed ataxia within 12 days after dosing. A further three were given single doses of 100 mg./kg. body weight and all showed ataxia within 10 days. There was, however, no toxic effect when 50 mg./kg. body weight was given. This substance is therefore markedly toxic. Di-*ortho*-propylphenyl mono-*para*-tolyl phosphate was given in two experiments to six birds. Four birds were given 500 mg./kg. body weight in five consecutive doses and two were given 500 mg./kg. body weight in four consecutive doses. All birds showed ataxia within 10 days. It is most probable that the slight toxicity of TXP is due to the presence of small amounts of mixed esters containing one *ortho*-propylphenyl group.

The Effect of 3 : 5-dimethylphenol.—Although it was shown that a phosphate ester containing one *ortho*-propylphenyl group is markedly toxic, this statement must be qualified. Mono-*ortho*-propylphenyl di-3 : 5-dimethylphenyl phosphate was synthesized and given to five chickens in single doses of 1,000 mg./kg. body weight. The birds were unaffected by the ester although one developed fowl paralysis. Next, five consecutive daily doses of 500 mg./kg. body weight were given to three birds all of which remained normal. The conclusion reached is that the 3 : 5-dimethylphenyl group counteracted the toxicity of the *ortho*-propylphenyl group.

In order to investigate the effect of the 3 : 5-dimethylphenyl group further, mono-*ortho*-tolyl-di-3 : 5 dimethylphenyl phosphate and mono-*ortho*-ethylphenyl-di-3 : 5-dimethylphenyl phosphate were synthesized. They were tested for toxicity by Barnes (1960). A single dose of 1,000 mg. of mono-*ortho* - tolyl - di - 3 : 5-dimethylphenyl phosphate/kg. body weight was given to two hens, one of which became severely, and the other moderately, ataxic. A dose of 500 mg./kg. gave rise to no signs in 16 days in a further two birds.

Mono-*ortho*-ethylphenyl-di-3 : 5-dimethylphenyl phosphate was given in a single dose of 1,000 mg./kg. body weight to two birds and both became severely paralysed. Half this dose caused mild ataxia in a further bird but no effect in another. It can be concluded that the 3 : 5-dimethylphenyl group reduces the toxicity of the *ortho*-substituted phenyl groups considerably. Henschler (1959) came to the same conclusion.

Phosphate Ester made from a Xylenol Fraction Free from *ortho*-cresol, *ortho*-ethylphenol and *ortho*-propylphenol ("NTP").—In order to prepare a non-toxic plasticizer it seemed to be necessary to remove from the raw material not only *ortho*-cresol and *ortho*-ethylphenol but also *ortho*-propylphenol.

The raw material for the production of TXP has a boiling range from 215° to 230°C. If we could prepare a material by careful fractionation which has a boiling range from 217° to 230°C. it would reduce the amount of *o*-propylphenol in the fraction to a very small quantity. (Phenols boiling above 230° C. were not included in the fraction because they give rise to coloured phosphate esters.) Such a phenolic fraction was prepared first in the laboratory and later on in the plant and is shown in Table 1. This fraction was reacted with phosphorus oxychloride in the presence of a catalyst to form the phosphate ester which is an oily colourless liquid.

This phosphate ester, subsequently termed "non-toxic plasticizer-NTP", was subjected to a variety of toxicity tests in a large number of animals. Batches from the laboratory and the plant were fed in varying doses, principally to chickens and rats, but also to a number of other animals including the rabbit, which is known to be sensitive to TTP. Table 4 shows that more than 100 chickens have been given doses of NTP ranging between 1,000 mg./kg. to 25,000 mg./kg. body weight. Fifteen birds were examined histologically with no abnormal findings. Six chickens were injected intraperitoneally with 1,000 mg./kg. body weight of NTP without clinical effect. The other animals examined (one dog, rabbit, guinea pig, hamster, four cats and 36 rats) were each given single doses of 5,000 mg./kg. body weight without detrimental effect. Rats can tolerate 10,000 mg./kg. body weight without causing any clinical effects.

Cholinesterase estimations of blood and brain were carried out on a variety of animals. In chickens there was an invariable drop of up to 80% in the plasma cholinesterase in the first 24 hours, which returned to normal over the next few days even when dosing was continued. In rats the plasma cholinesterase was either lowered very slightly by NTP or was unaltered. An account of these investigations by one of us (A.N.W.) is being prepared for publication elsewhere.

Tri-*meta*- and tri-*para*-ethylphenyl Phosphate.—It has been found previously that the phosphate esters of 3 : 5-dimethylphenol and 3 : 4-dimethylphenol are non-toxic, and we decided to test the phosphate esters of the other compounds present in the raw material. From synthetic materials we prepared tri-*meta*-ethylphenyl phosphate and tri-*para*-ethylphenyl phosphate.

We gave six birds 5 × 500 mg./kg. body weight of tri-*meta*-ethylphenyl phosphate. All the birds remained healthy and two were histologically examined with negative findings. Two birds were given a single dose of 1,000 mg./kg. body weight with some doubtful effects, but histological examination also gave negative findings. Three further birds were given a single dose of 1,000 mg./kg. They remained completely well, two were examined histologically, both with negative results. We concluded that tri-*meta*-ethylphenyl phosphate is non-toxic.

We dosed 30 birds in several batches with tri-*para*-ethylphenyl phosphate from 5 × 500 mg./kg. down to single doses of 200 mg./kg. body weight. In all cases the birds were paralysed and histological examination confirmed that there was demyelination. This finding is contrary to the working hypothesis we had formed, namely, that only a phosphate ester made from a compound with one substituent group in the *ortho* position is toxic; in this case a phosphate ester with ethyl groups in the *para* position is also toxic. This is a surprising finding because a tri-*para*-tolyl phosphate is definitely not toxic.

Mixed Esters Containing One or Two *para*-ethylphenyl Groups.—We had to reconsider the reasons for the lack of toxicity in the "non-toxic plasticizer". It has been shown that the raw material we prepared for this plasticizer contained 10% of *para*-ethylphenol and despite this the phosphate ester was non-toxic. We thought originally that this was due to there not being enough of the phosphate tri-ester of *para*-ethylphenol present to cause toxicity at the dose level of 2,500 mg./kg. Birds were therefore dosed with 10 times this dose, namely, 25,000 mg./kg. body weight but even then no toxic effect was found.

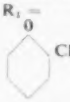
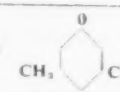
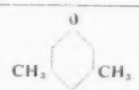
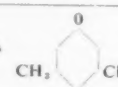
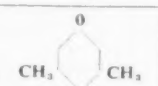
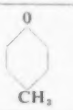
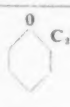
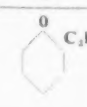
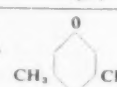
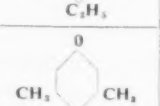
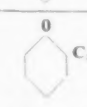
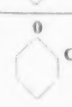
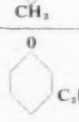
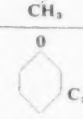
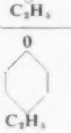
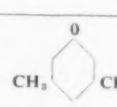
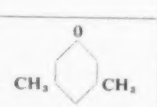
We considered next that in the non-toxic phosphate ester, the tri-*para*-ethylphenyl phosphate is unlikely to be present, and that the *para*-ethylphenyl group will only be present in mixed esters having one or possibly two *para*-ethylphenyl groups attached to the phosphate radical. This was substantiated by the addition of 10% tri-*para*-ethylphenyl phosphate to the non-toxic phosphate esters and we found that this mixture became toxic.

We prepared the following esters (see Table 3): mono-*para*-ethylphenyl di-*p*-tolyl phosphate was given to 15 birds in the following doses/kg. body weight. Three birds in each group received 5 500 mg.; 5 × 1,000 mg.; 7 × 1,000 mg.; single doses of 2,500 mg., and a single dose of 1,000 mg. intraperitoneally. One bird died of egg peritonitis and one of lymphomatosis but all the other birds remained well. One of the healthy birds was killed, examined histologically and no demyelination was seen. Post-mortem examinations on the two sick birds revealed the cause in each case.

Mono-*para*-ethylphenyl di-3 : 5-dimethylphenyl phosphate was given to seven birds. Four received 5 × 500 mg. and three 1,000 mg./kg. body weight. At this time lymphomatosis occurred in some of the birds and the results did not give a clear picture but post-mortem and histological examinations showed no toxic effects due to the phosphate ester. The experiment was repeated on 12 birds in the following doses/kg. body weight: three received 5 × 500 mg.; three 4 × 1,000 mg.; three 7 × 1,000 mg. and three were injected intraperitoneally with a single dose of 1,000 mg. In all cases the birds remained healthy. One bird was examined histologically and found to be normal.

TABLE 3

PHYSICAL CONSTANTS AND TOXICITY OF UNSYMMETRICAL TRI-ARYL PHOSPHATES

Compound	Structural Formula $R_3-\overset{\overset{O}{\vert}}{P}-R_1$ (R_2)	Toxicity (ataxia in chickens)	Refractive Index (n_D^{20})	Boiling Point at 1 mm.Hg (°C.)
Mono-*o*-tolyl di-*p*-tolyl phosphate (*a*)	R_1 =  R_2 = R_3 =	+	1·5576	223·5-225·5
Mono-*o*-tolyl di-3 : 5-dimethyl-phenyl phosphate (*a*; *b*)	 	+	—	229-231 (m.p. 66·8 °C.)
Mono-*o*-ethylphenyl di-*p*-tolyl phosphate (*a*)		+	1·5547	237·5-239·5
Mono-*o*-ethylphenyl di-3 : 5 dimethylphenyl phosphate (*a*; *b*)	 	+	1·5510	242-244
Di-*o*-ethylphenyl mono-*p*-tolyl phosphate (*a*)	  	+	1·5520	228-230
Mono-*o*-*n*-propylphenyl di-*p*-ethyl phenyl phosphate (*a*)		+	1·5448	249·5-251·5
Mono-*o*-*n*-propylphenyl di-3 : 5-dimethylphenyl phosphate (*a*)	 	+	1·5478	244-246
Di-*o*-*n*-propylphenyl-mono-*p*-tolyl phosphate (*a*)	 	+	1·5432	237-239
Mono-*p*-ethylphenyl di-*p*-tolyl phosphate (*a*; *b*)		+	1·5533	241-243 (m.p. 35 °C.)
Di-*m*-ethylphenyl-mono-*p*-ethyl-phenyl phosphate (*a*)	 	+	1·5480	241-243
Mono-*p*-ethylphenyl di-3 : 5-dimethylphenyl phosphate (*a*; *b*)	  	+	1·5500	245·5-247·5 (m.p. 68·5 °C.)
Di-*p*-ethylphenyl mono-*p*-tolyl phosphate (*a*)		+	1·5510	244-246
Phosphate ester from last 4% of NTP xylenols (*a*; *c*)		+	1·5478	250-260

Notes.—(*a*) Purified by fractional distillation; (*b*) Recrystallized to constant melting point; (*c*) Phenolic raw material was the 4% highest boiling fraction of NTP xylenols.

Other raw materials were as described in Table 2, with the addition of 3, 5-dimethyl phenol (*b*), m.p. 64 °C.

Di-*para*-ethylphenyl mono-*para*-tolyl phosphate was given to four birds at a dose level of 5 × 500 mg./kg. and four birds received a single dose of 1,000 mg./kg. body weight. In all cases the birds remained healthy. Similarly we found di-*meta*-ethylphenyl mono-*para*-ethylphenyl phosphate to be non-toxic at this dose level in six birds.

We concluded from these experiments that mixed esters containing one or two *para*-ethylphenyl groups may be non-toxic, unless *ortho*-alkylphenyl groups are present in the molecule. Since *ortho*-cresol, *ortho*-ethyl phenol and *ortho*-propylphenol are absent from the starting material, such toxic esters cannot be formed.

Tri-2-methyl-4-ethylphenyl Phosphate.—We tested another compound which is present in the raw material and which is of particular interest because it has an ethyl group in the *para* position and a methyl group in the *ortho* position, namely, 2-methyl-4-ethylphenol. The phenol was synthesized and the phosphate tri-ester formed and given to six birds in five doses of 500 mg./kg. body weight. All six birds remained well and the ester is considered to be non-toxic.

Other Phenols.—Of the phenols 4% boil between 228° and 230°C. They are a mixture of methylethylphenol, dimethylethylphenol and *iso*propylphenol. We concentrated these phenols in one fraction and formed the phosphate ester from it. In two experiments 10 birds were given 5 × 500 mg./kg. body weight of this phosphate ester. One bird died of atypical symptoms presumed to be due to lymphomatosis but all the other birds remained healthy. We concluded that this phosphate ester is non-toxic. Our findings, with some chemical and physical properties of the pure esters, are summarized in Tables 2 and 3.

Conclusions

Previous workers have established that the toxicity of commercial samples of tritolyl phosphate (TTP) is due to the presence of phosphate esters containing the *ortho*-tolyl (*ortho*-methylphenyl) group. Henschler has claimed that esters which contain only one such group per molecule are the most toxic.

The present series of experiments has shown that even when all *ortho* cresol is removed from the phenolic starting materials, the resulting TTP is still toxic. Experiments with pure esters of known structure have shown that the toxicity is not due to the presence of dialkyl substituted phenyl groups (even where one alkyl substituent is *ortho* to the phenolic hydroxyl, as in tri-2 : 4 and 2 : 5-dimethylphenyl phosphate), since such esters are not toxic in the doses we used.

Mono-*ortho* ethylphenyl di-*para*-tolyl phosphate or di-*ortho*-ethylphenyl mono-*para*-tolyl phosphate are toxic. As in the case of the *ortho*-tolyl phosphates, the mixed esters are more toxic than the tri-ester (tri-*ortho*-ethylphenyl phosphate), the latter being non-toxic to chickens at a dose level of 2,500 mg./kg. body weight. A phenolic fraction from which all the *ortho*-cresol and the *ortho*-ethylphenol has been removed has produced a TTP of a very low

TABLE 4

TOXICITY TESTS OF NON-TOXIC PLASTICIZER (NTP) IN CHICKENS

Batch Number *	Number of Chickens	Dose mg./kg.	Neurotoxic Signs	
			Clinical	Histological
1853	7	5 × 500	5 negative†	
1854	34	5 × 500	34 negative	8 negative
1854/1	6	5 × 500	6 negative	2 negative
1854/1	4	5 × 5,000	4 negative	
1854	12 in four batches (4, 4, 2, and 2)	4: 1 × 5,000	4 negative‡	
		4: 1 × 2,500	3 negative	
		2: 1 × 1,000	2 negative	
		2: 1 × 500	2 negative	
3304	28	5 × 500	3 behaved abnormally but no specific findings: one of these had coccidiosis	2 of the 3 birds behaving abnormally were examined histologically-negative; 3 others negative
			25 negative	
3304	6	1 × 1,000 intraperitoneally	6 negative	
3333	11 in three batches (6, 3, and 2)	6: 5 × 500	6 negative	
		3: 1 × 1,000	3 negative	
		2: 5 × 5,000	2 negative	
3334	8 in three batches (3, 3, and 2)	3: 5 × 500	3 negative	
		3: 1 × 1,000	3 negative	
		2: 5 × 5,000	2 negative	

*1853: Phenolic fraction and phosphate ester prepared in laboratory; 1854: Phenolic fraction made on plant, ester made in laboratory; 1854/1: A second batch of phenolic fraction made on plant, ester made in laboratory; 3304: Phenolic fraction and ester made on plant; 3333: Second batch made on plant; 3334: Third batch made on plant.

†Two non-specific deaths. ‡One non-specific death.

Footnote.—Period of observation was 30 days or more in each case. Several chickens were observed for many months after dosing and lack of toxicity was confirmed.

order of toxicity. This residual toxicity is probably due to the fact that not all the *ortho*-ethylphenol has been removed. A TTP made from a synthetic mixture of *meta*-cresol, *para*-cresol and 2 : 4 and 2 : 5 dimethylphenol proved to be non-toxic. If, in the preparation of trixylenyl phosphate, all *ortho*-cresol and all *ortho*-ethylphenol is removed, the resulting TXP is still slightly toxic. This residual toxicity has now been attributed to the hitherto unsuspected presence of *ortho*-propylphenol in the raw material, and mixed esters containing the *ortho*-propylphenyl group have, with one exception, also proved to be toxic.

Removal of *ortho*-cresol and *ortho*-ethyl and *ortho*-propyl-phenols from a mixed xylenol fraction has given a phenolic mixture from which a non-toxic phosphate ester (NTP) has been prepared. NTP has been fed to chickens in doses ranging from 1,000 mg./kg. to 25,000 mg./kg. body weight, without the appearance of any toxic symptoms (Table 4). Long-term feeding experiments are in progress, and it is apparent that those on very high doses (5,000 p.p.m. in the diet) have not thrived as well as the controls and show some changes in the central nervous system which are the subject of further study (Cavanagh, 1960).

Surprisingly tri-*para*-ethylphenyl phosphate (unlike tri-*para*-tolyl phosphate) is toxic, in doses as low as 200 mg./kg. body weight. On the other hand mixed esters containing one or two *para*-ethylphenyl groups are non-toxic. This finding is so completely at variance with that of the *ortho*-alkylphenyl esters described above, that it might suggest a different toxic mechanism in the two cases, though there is as yet no evidence, either from macroscopic or microscopic study of the affected chickens, that this is so.

Tri-2-methyl-4-ethylphenyl phosphate, which contains *para*-ethyl and *ortho*-methyl substituents in the same benzene ring, has been tested and found non-toxic at the 2,500 mg./kg. level.

The 3 : 5-dimethylphenyl group markedly reduced the toxic effect of the mono-*ortho*-alkyl groups, thus mono-*ortho*-tolyl-di-3 : 5-dimethylphenyl phosphate and mono-*ortho*-ethylphenyl di-3 : 5-dimethylphenyl phosphate are less toxic than other mixed esters containing the *ortho*-tolyl or the *ortho*-ethylphenyl group. The effect of the 3 : 5-dimethylphenyl group is strongest in mono-*ortho*-propylphenyl di-3 : 5-dimethylphenyl phosphate because this compound proved to be non-toxic.

The authors wish to thank the Directors of Coalite and Chemical Products Limited, and Albright and Wilson Limited for their generous support in this research.

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Brit. J. industr. Med., 1960, **17**, 201.

AEROSOL INHALATION OF $CaNa_2E.D.T.A.$ (MOSATIL) BY WORKERS CONSTANTLY EXPOSED TO LEAD POISONING

BY

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(RECEIVED FOR PUBLICATION AUGUST 11, 1959)

An aerosol of $CaNa_2E.D.T.A.$ ("mosatil") has been administered in hospital to two groups of five men who had been working on a lead smelter and exposed to lead in air concentrations of the order of 0·6 to 1·25 mg. of lead per m^3. Five patients each inhaled 0·6 g. of $CaNa_2E.D.T.A.$ on seven successive days, and 2·4 g. on the ninth day. An average of 21·6 mg. of lead was excreted during the treatment.

Five patients given 2·4 g. of $CaNa_2E.D.T.A.$ every other day for eight days excreted an average of 14·2 mg. of lead each during treatment. The urinary coproporphyrin level fell to normal in both groups.

In recent years aerosol therapy has found an increasing use. Its advantage is that the fine aerosol particles are absorbed directly from the lungs into the blood stream through the alveolar epithelium without discomfort to the patient, and it can be given simultaneously to groups of patients. Alkaline mineral waters have been used in this way for silicosis (Beckmann and Reif, 1955). The disadvantages of aerosol therapy are the need for special equipment and the uncertainty about the dose received by the patient. Sometimes drying of the mucous membranes may be uncomfortable for the patient.

The value of $CaNa_2E.D.T.A.$ in the treatment and prevention of lead poisoning is well recognized (Teisinger and Srbová, 1956; Buckup and Remy, 1958; Unseld, 1958). It may also be used as a diagnostic test (Albahary, Truhaut, and Boudène, 1958; Savićević, Petrović, Stanković, and Djordjević, 1959). Teisinger and Srbová (1956) have already reported favourably on the use of $CaNa_2E.D.T.A.$ aerosols. Four patients were given 5 ml. 10-20% $CaNa_2E.D.T.A.$ three times daily with breaks over a period of 19 days. The blood lead and urinary coproporphyrin levels were reduced and clinical symptoms disappeared.

Method

Solutions of $CaNa_2E.D.T.A.$ ("mosatil") were given to 10 patients as an aerosol generated by a Draeger aerosol apparatus. The patients were working in a smelting plant with an atmospheric concentration of 0·6-1·25 mg. lead oxide per m^3. During treatment the nasal mucosa became dry and this was attributed to the warm air from the apparatus and the high Ca content of the drug.

Five patients received 0·6 g. $CaNa_2E.D.T.A.$ (5 ml. "mosatil") daily for seven days and on the ninth day 2·4 g. $CaNa_2E.D.T.A.$ (10 ml. "mosatil forte"). The total dose was 6·6 g. $CaNa_2E.D.T.A.$ Five patients received four doses of 2·4 g. $CaNa_2E.D.T.A.$ on alternate days, a total of $CaNa_2E.D.T.A.$ 9·6 g.

All the patients were in hospital during treatment and for the two subsequent days. Daily analyses were carried out of the urinary lead and coproporphyrin and a haematogram including stippled cells and reticulocytes was drawn. Blood lead was determined two to three times during the period of treatment.

Results

In Fig. 1 the values for urinary lead and coproporphyrin in the first group are shown. The excretion of lead rises as soon as inhalation therapy starts, drops sharply when it is discontinued, and rises when it is resumed. The daily fluctuations in lead excretion related to treatment on alternate days is shown more strikingly in the second group (Fig. 2). The total lead excreted falls steadily and remains at a constant low level for the three days after treatment stopped. Urinary coproporphyrin shows a fall in both groups. Blood lead levels, originally

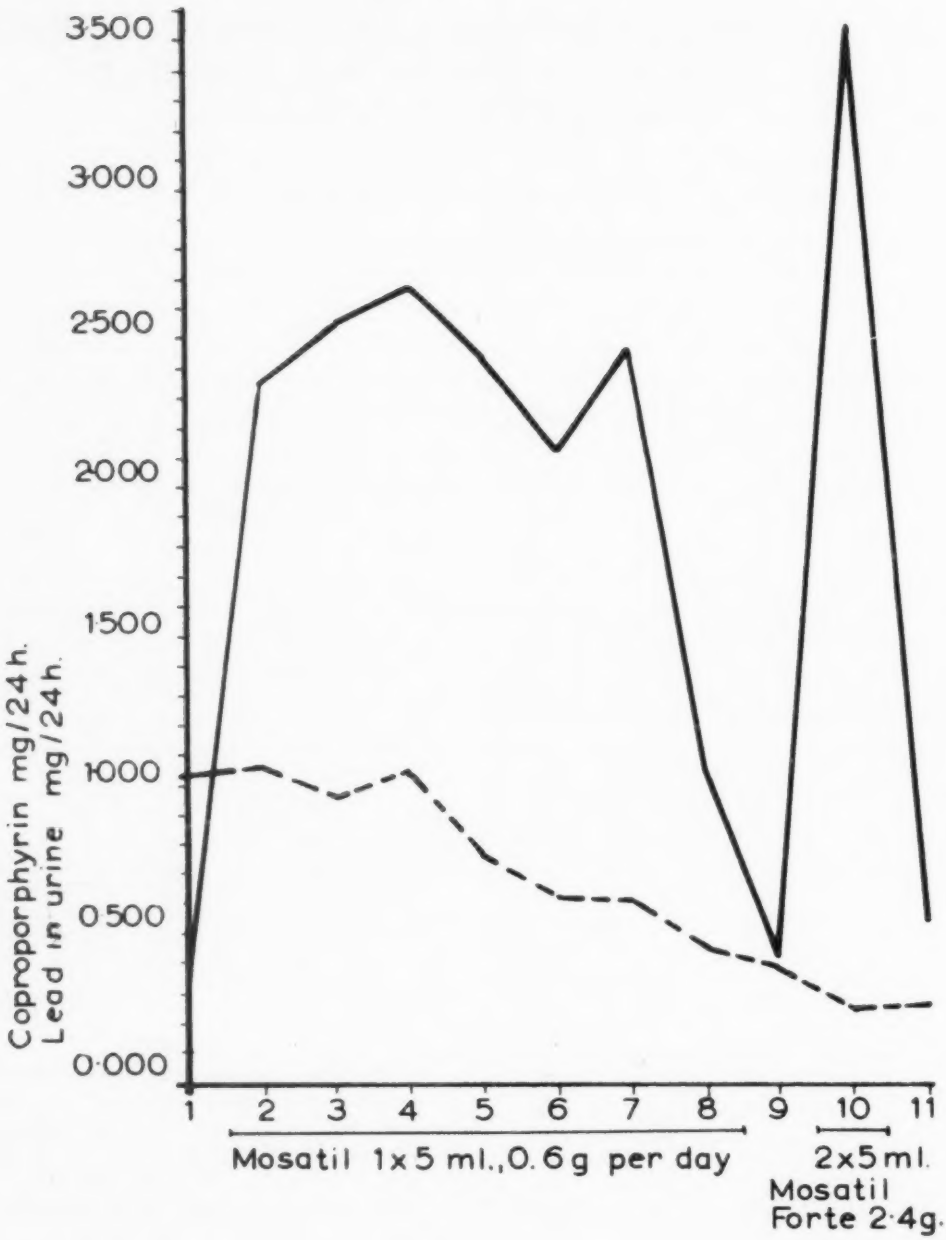

FIG. 1.—The excretion of lead (continuous line ————) and coproporphyrin (broken line - - - - -) in the urine of men receiving $CaNa_2E.D.T.A.$ by inhalation on successive days.

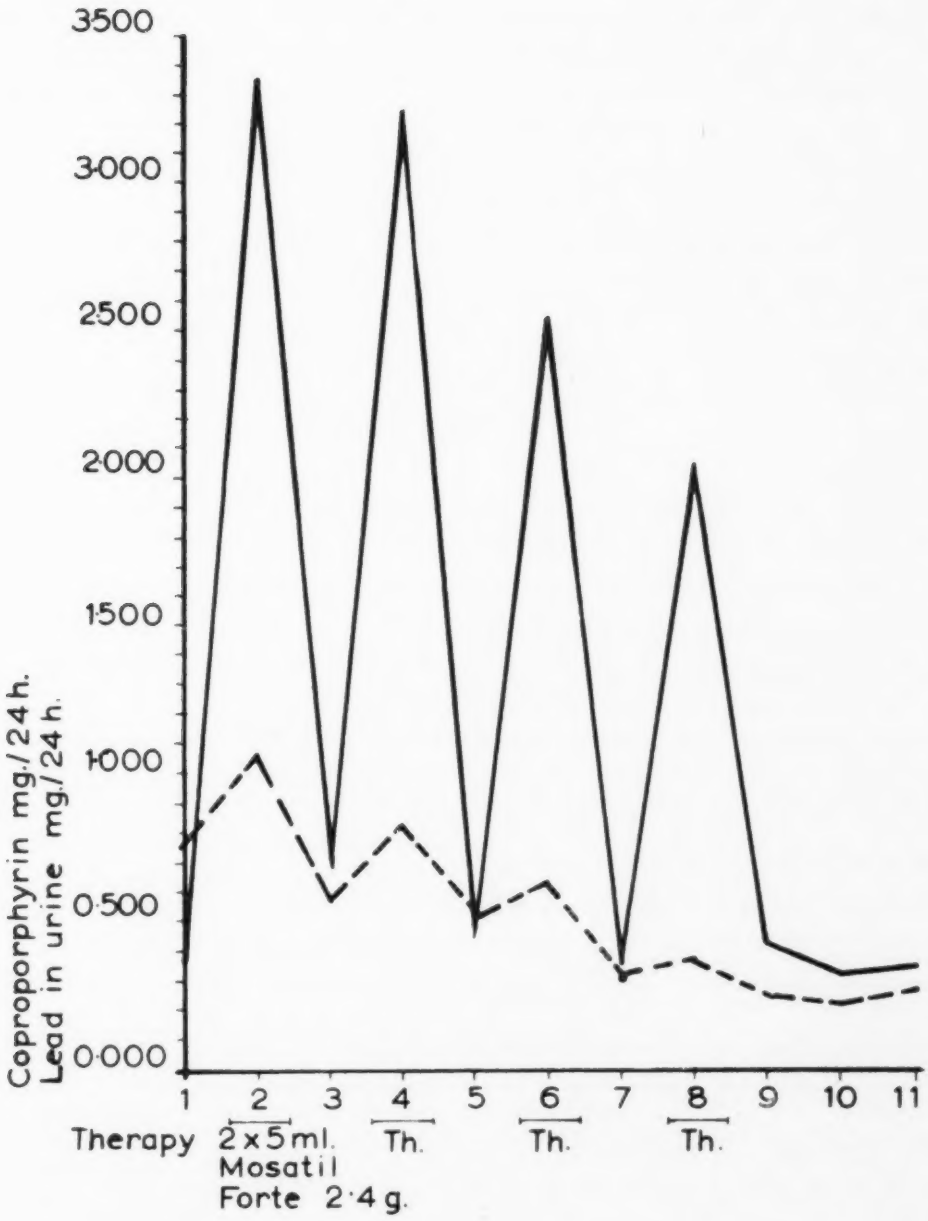

FIG. 2.—The excretion of lead (continuous line ———) and coproporphyrin (broken line - - - - -) in the urine of men receiving $CaNa_2E.D.T.A.$ by inhalation on alternate days.

0·1 mg./100 ml., fell by 20 to 45% during treatment in both groups.

Stippled cell counts showed some irregularity during the course of treatment but there was no other change in the blood picture.

The absorption of E.D.T.A. during aerosol inhalation has been studied. Preliminary observations show that individuals vary in the degree to which they absorb E.D.T.A. but for a given subject the value is fairly constant and lies between 10 and 30% of the dose administered.

However, the first group receiving only 6·6 g. E.D.T.A. excreted on the average 21·6 mg. Pb while the second group receiving 9·6 g. E.D.T.A. excreted only 14·2 mg. This difference may be due to the fact that the first group received continuous treatment but the second received E.D.T.A. on alternate days.

Conclusion

The administration of $CaNa_2E.D.T.A.$ by aerosol therapy increases the urinary excretion of lead. If evidence can be obtained that the long-term administration of E.D.T.A. itself carries no risk, it may have a use in the preventive treatment for exposed workers. Daily inhalations seem to be more effective than intermittent administration. Further work is needed on the absorption of $CaNa_2E.D.T.A.$ given by various routes.

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THE APRIL (1960) ISSUE

The April (1960) issue contains the following papers:—

Dust Content, Radiology, and Pathology in Simple Pneumoconiosis of Coalworkers—

Part I: General Observations. By D. Rivers, M. E. Wise, E. J. King, and G. Nagelschmidt.

Part II: Detailed Analysis of the Data. By D. Rivers and M. E. Wise.

Pneumoconiosis in Makers of Artificial Grinding Wheels, Including a Case of Caplan's Syndrome. By E. Posner.

A Study of the Repeatability of Ventilatory Tests, Anthropometric Measurements, and Answers to a Respiratory Symptoms Questionnaire in Working Coal-miners. By J. R. Ashford, G. D. Forwell, and R. Routledge.

A Study of the Reproducibility of the Forced Vital Capacity of Coalworkers at Two Collieries in Scotland and Two Collieries in South Wales. By D. P. Duffield and J. R. Ashford.

Antiseptic Cream for Use on the Hands in Food Establishments. By Doreen L. Wedderburn.

Oil Folliculitis: A Study of 200 Men Employed in an Engineering Factory. By J. S. Finnie.

Studies on the Chemical Forms of Urinary Lead. By G. T. Dinischiotu, B. Nestorescu, I. C. Radulescu, C. Ionescu, N. Preda, and G. Ilutza.

Effects of Chronic Dieldrin Ingestion on the Muscular Efficiency of Rats. By Mélèk Khaïry.

The Failure of Absorption of DC Silicone Fluid 703 from the Gastrointestinal Tract of Rats. By J. Paul and W. F. R. Pover.

The Origin of the Term "Pneumonokoniosis". By A. Meiklejohn.

Obituary: Dr. Sydney Henry.

Book Reviews.

A number of copies are still available and may be obtained from the Publishing Manager, British Medical Association, Tavistock Square, W.C.1, price 17*s.* 6*d.*

Brit. J. industr. Med., 1960, **17**, 205.

A BIOCHEMICAL STUDY OF THE URINARY PROTEIN OF MEN EXPOSED TO METALLIC MERCURY

BY

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(RECEIVED FOR PUBLICATION FEBRUARY 8, 1960)

Proteinuria is not usually reported in chronic mercury poisoning. The urine of three men exposed to metallic mercury vapour was found to contain protein. In two, the proteinuria disappeared on removal from exposure. The urinary protein in two cases was investigated and found to be indistinguishable from serum protein by the criteria used. The bound carbohydrate values were similar to those found in nephritic urinary protein. One man was diagnosed clinically as a chronic nephritic over a year after removal from exposure. It would be premature to connect this condition with the preceding exposure to mercury.

Proteinuria is not a frequent finding in chronic mercury poisoning. None of a previous group of mercury workers examined for urinary amino-acids (Clarkson and Kench, 1956) showed proteinuria. A further small group of workers was subsequently brought to our notice all of whom were passing protein in the urine. The urinary protein was predominantly globulin on electrophoresis, exhibiting a pattern similar to that given by the low molecular weight cadmium urinary protein (Smith, Wells, and Kench, 1960). An examination of the mercury urinary protein was made to provide information on the modification of the normal protein economy of the body due to mercury.

Medical Data

Three men were exposed to metallic mercury vapour in their work over a period of two years, when it was discovered that their urine contained protein. In one of the men the amount was relatively small (M3) and rapidly disappeared on his removal from exposure. He was not examined further. The other two men behaved differently on removal from contact with mercury. One man (M1) continued to pass protein in small amounts for some three months. The other man (M2) continued to pass protein, which was different in electrophoretic pattern during and after exposure; the proteins were denoted M2A and M2B respectively (Fig. 1). This patient was investigated in hospital seven months after his exposure to mercury ceased. Clinical details are as follows:—

He complained of no symptoms but his urine contained protein which varied in quantity from day to day.

Blood pressure was 180/120 mm. Hg; it settled with rest to 160/105.

Urine was sterile, containing casts but no pus.

A straight radiograph of the urinary tract and an intravenous pyelogram excluded an opaque calculus. Both kidneys appeared to function well and outlined normally.

The serum sodium test was 141 mEq./litre, serum potassium 5·7 mEq./litre, serum Cl 104 mEq./litre, serum HCO_3 24 mEq./litre, blood urea 36 mg./100 ml., and urea clearance 79% of the average normal.

Materials and Methods

Twenty-four hour samples of urine were obtained from these men and transported to the laboratory with the least possible delay. The following investigations were carried out on the urine.

Urinary Mercury.—The concentration of mercury in the urine was determined by the permanganate oxidation and dithizone (diphenylthiocarbazone) method of Milton and Hoskins (1947).

Urinary Amino-acids.—These were analysed by the two-dimensional paper chromatographic procedure described by Clarkson and Kench (1956) using methanol : water : pyridine (80 : 20 : 4 by vol.) and ethyl methyl ketone: *tert*-butanol : water : diethylamine (40 : 40 : 20 : 4 by vol.).

Protein.—Urinary protein concentration was measured by a modification of the biuret method of Hiller, McIntosh, and Van Slyke (1927).

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The protein was prepared in a form suitable for analysis by dialysis in cellophane sacs overnight against running tap water and subsequently against distilled water for three to four hours. The protein was then obtained by freeze-drying. It was brown due to urinary pigment which was undialysable.

Electrophoresis.—The electrophoretic behaviour of the protein was examined by the ridgepole technique of Durrum (1950); the protein was located with azo-carmine B (Plückthun and Götting, 1951) and the profiles derived with an EEL "scanner".

The proteins were also examined by zone electrophoresis on acetyl cellulose columns (Campbell and Stone, 1956). The components thus separated from 150 mg. of freeze-dried whole protein were checked for homogeneity by paper electrophoresis and then prepared individually for analysis by dialysis and freeze-drying.

Carbohydrate Content.—Whole protein was hydrolysed with N H_2SO_4 in sealed tubes (Consden and Stanier, 1952). Descending chromatography (Jermyn and Isherwood, 1949) with ethyl acetate : pyridine : water (40 : 20 : 40 : by vol.) was employed and the sugars detected by spraying with aniline phthalate (Partridge, 1948). The sugars were measured by determination of the areas of the spots (Fisher, Parsons, and Holmes, 1949).

Protein-bound Hexose.—The distribution of the hexose between the electrophoretic components was measured by the orcinol (5-methylresorcinol) procedure of Weimer and Moshin (1953). A 2 : 1 mixture of galactose and mannose was employed as a standard.

Amino-acid Composition.—Each electrophoretic component was hydrolysed with 6N HCl according to Block (1951). The amino-acids thus derived were dissolved in 10% *iso*propanol and applied directly to the paper and analysed in the same way as were the free urinary amino-acids.

Ultracentrifuge Measurements.—Samples of the freeze-dried proteins were dissolved in phosphate-NaCl buffer *p*H 8·0 (K_2HPO_4 0·0044M, Na_2HPO_4 0·0652M, NaCl 0·15M) and dialysed for about 24 hours at 4°C. against a large volume of the same buffer. The refractive increment due to protein in the dialysed solutions was determined with a dipping refractometer (λ = 546 mμ). By diluting with buffer, solutions having a refractive increment due to protein of 0·00200 were prepared and these were examined in the Svedberg oil-turbine ultracentrifuge in a 12 mm. cell at approximately 250,000 g. Optical observations by the diagonal Schlieren method (Philpot, 1938) were photographically recorded on Ilford half-tone panchromatic plates, using a high-pressure mercury arc as a light source from which monochromatic light (λ = 546 mμ) was isolated by a suitable filter. Distances on the plates were determined with a measuring microscope reading to 0·001 mm. and sedimentation coefficients were computed by the method of Cecil and Ogston (1948).

Immunology.—This was carried out by the tube precipitin method of Oakley and Fulthorpe (1953) using rabbit antiserum prepared against proteins of whole normal human serum.

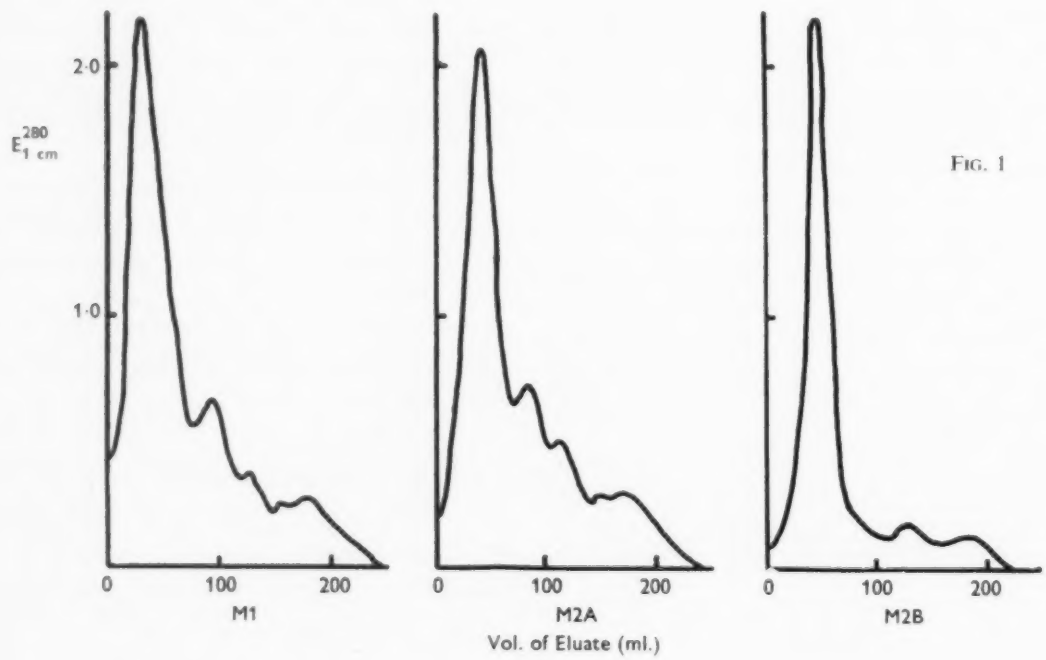

FIG. 1

Results

The concentrations of mercury and protein in the urine of the three men studied are presented in Table 1. The urinary proteins were completely coagulable by heat.

The urinary proteins from both men exhibited similar electrophoretic behaviour on paper with a preponderance of globulin. This changed markedly in the case of M2, following removal from exposure, to a pattern showing little globulin. A similar picture was presented by acetyl cellulose column electrophoresis (Fig. 1), except that a minor component, not fully resolved, appeared in the β-globulin region.

TABLE 1

CONCENTRATIONS OF MERCURY AND PROTEIN IN URINE OF MEN EXPOSED TO METALLIC MERCURY

Workman	Mercury (μg./l.)	Protein (g./l.)
M 1	180	1·3
M 2A	430	1·6
M 2B	—	0·8
M 3	990	0·3

The urinary mercury concentrations of men with no known exposure to mercury were given as 0-90μg./24 hr. by Buckell, Hunter, Milton, and Perry (1946).

The nature of the protein-bound carbohydrate was investigated by paper chromatography of hydrolysates of the total urinary protein. Galactose, glucose, mannose, fucose, and ribose were detected and their presence confirmed by the use of alternative solvent systems. The results are presented in Table 2. The distribution of hexose between the electrophoretic fractions is shown in Table 3.

In every case the urinary free amino-acids determined were within the normal limits as found by Clarkson and Kench (1956).

The amino-acid composition of the electrophoretic components is given in Table 4. For comparison only the eight most accurately measured amino-acids were taken and each value expressed as a percentage total of eight.

In the ultracentrifuge the total urinary proteins

TABLE 3

HEXOSE CONTENT OF ELECTROPHORETICALLY SEPARATED COMPONENTS OF MERCURY URINARY PROTEINS

Nature of Protein*	Total Protein	Electrophoretic Component†			
		1	2	3	4
M 1	41	19	38	24	—
M 2A	37	17	38	21	—
M 2B	29	15	—	19	12
UN 1	31	14	31	22	12
UN 2	33	12	—	24	13

*As in Table 2.
†The hexose values were determined by reference to a galactose-mannose 2 : 1 standard and are expressed as mg./g. protein (biuret). Each figure is the mean of two readings.

(M1, M2A, M2B) each sedimented as a single symmetrical peak having the following sedimentation coefficients respectively ($S_{20, w}$, approximately 1% solution), M1, 4·03S; M2A 4·16S; M2B, 4·04S. These values correspond closely with the value given by a 1% solution of human serum albumin.

Immunologically the mercury urinary proteins exhibit multiple precipitin reactions with rabbit anti-total human serum protein. This was assumed to indicate similarity of antigenic structure to serum and nephritic urinary proteins which gave an equally complex pattern.

Discussion

The urinary protein investigated was associated with absorption of mercury. It is known that none of the men exhibited proteinuria before exposure to mercury and removal from exposure resulted in the cessation of proteinuria in two cases and in a reduction of the protein excretion in the third. The last case also showed a marked change in the electrophoretic pattern of the protein, most notable being the disappearance of the large component with the mobility of α_2 globulin. The mercury urinary protein was separable on electrophoretic analysis into five components. The first three, corresponding to albumin, α_2, and β globulin, were sufficiently well differentiated to allow their isolation

TABLE 2

RELATIVE PROPORTIONS OF MONOSACCHARIDES BOUND TO URINARY PROTEINS FROM MERCURY WORKERS AND FROM NEPHRITIC PATIENTS

Nature of Protein	No. of Analyses	Galactose	Glucose	Mannose	Fucose	Ribose
M 1†	7	32*	9	23	30	6
M 2A	6	30	9	25	29	7
M 2B	6	35	9	21	30	5
UN 1	6	38	11	19	27	5
UN 2	5	36	9	20	30	4

*All figures are expressed as a percentage of the total monosaccharide found in the unfractionated protein and are arithmetic means of the results of the individual analyses. The standard deviation of the readings was 1·6 with 80 d.f.
†M 1 and M 2A = urinary protein from workmen during exposure to mercury
M 2B = urinary protein from M 2 after removal from exposure
UN 1 and UN 2 = urinary protein from two nephritic patients

TABLE 4

AMINO-ACID COMPOSITION OF ELECTROPHORETIC COMPONENTS OF MERCURY URINARY PROTEIN

Source of Protein	No. of Analyses	Electrophoretic Component	Arginine*	Lysine	Aspartic Acid	Glutamic Acid	Histidine	Glycine	Serine	Alanine
M 1	5	1	9·6	12·9	18·8	25·7	2·0	4·3	6·6	20·7
M 2A	2	1	9·2	14·4	20·3	25·4	2·7	5·6	6·3	16·2
M 2B	4	1	7·2	13·2	16·1	29·4	1·5	5·8	5·9	21·1
UN 1	3	1	8·7	14·6	18·3	24·4	2·1	7·1	8·5	16·4
UN 2	2	1	7·1	12·1	17·9	24·5	3·0	6·1	7·4	21·7
M 1	4	2	11·2	10·3	15·5	20·2	2·0	9·8	10·4	20·0
M 2A	3	2	9·6	10·2	17·4	19·0	2·5	12·1	11·0	18·2
UN 1	2	2	10·8	8·8	22·3	17·7	3·1	14·2	10·9	12·2
M 1	4	3	13·4	9·5	12·4	20·3	—	12·8	12·5	20·0
M 2A	2	3	11·8	10·3	14·8	15·6	—	13·7	13·5	19·2
M 2B	2	3	12·9	13·0	17·7	17·9	2·0	13·2	10·3	13·0
UN 1	2	3	9·0	10·4	18·1	17·2	2·3	12·1	18·4	12·4
UN 2	3	3	9·1	8·5	17·3	20·4	2·1	12·0	13·2	17·4
M 2B	2	4	9·9	8·3	16·4	16·1	—	13·1	19·3	16·9
UN 1	2	4	8·6	9·1	14·0	17·9	2·3	16·1	16·7	15·3
UN 2	2	4	9·9	8·6	14·3	22·9	2·0	14·0	14·5	11·2
Error† Variance			1·11 0·85	1·41 0·79	1·45 1·35	1·13 1·46	0·29 0·44	0·83 0·43	0·99 0·71	1·62 1·33

*The values for each amino-acid are expressed as a percentage of the total of the eight amino-acids measured in terms of α-amino nitrogen.
†Mean difference between 17 pairs (histidine 13 pairs) of duplicate readings.

for chemical analysis but the two components of lowest mobility, present only in small amounts, were not completely resolved and further examination was not feasible.

The molecular weight of the mercury urinary protein as deduced from ultracentrifugal analysis was very near to that of serum albumin. The component of electrophoretic mobility comparable with albumin was the biggest fraction. Amino-acid analysis of the components showed that each was indistinguishable in this respect from the components of nephritic urinary protein of corresponding electrophoretic mobility. The bound carbohydrate values were also very close to those for nephritic urinary protein and immunological similarities were apparent.

This evidence leads to the conclusion that in the men studied exposure to mercury resulted in the appearance of serum proteins in the urine. This protein had presumably traversed the kidney but it is not possible to confirm the mechanism by which this occurred. However, as the proteinuria ceased in two of the cases following removal from the mercury hazard the lesion would appear to have been, on this occasion, readily reversible.

The third man (M2) was diagnosed clinically as a chronic nephritic over a year after removal from exposure and the predominance of albumin in the urinary protein was in accordance with this finding. The evidence derived from the ultracentrifuge and amino-acid, carbohydrate, and immunological analyses is totally consistent with chronic nephritis. It would be premature to connect this condition with the preceding exposure to mercury.

We should like to thank Professor R. E. Lane, C.B.E., for his advice and clinical guidance throughout this study. Dr. R. A. Kekwick kindly carried out the ultracentrifugal studies. Our thanks are also due to Miss I. Dingwall Fordyce for all her help with the statistical aspects of the work and to Professor J. E. Kench for his continued interest.

This study was prompted by the observation of proteinuria in workman M3 by Dr. Spink of Blackburn who kindly brought the finding to our notice.

The Medical Research Council generously supported these studies with grants to the authors.

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A SIMPLIFIED METHOD FOR THE ESTIMATION OF NICKEL IN URINE

BY

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(RECEIVED FOR PUBLICATION APRIL 15, 1959)

A simplification of Sandell's method for estimating nickel in urine is described. Nickel is a normal constituent of most articles of food and between 0·01 and 0·03 p.p.m. are found in normal urine. There is a slight increase of urinary nickel in workers engaged in the carbonyl process. After accidental inhalation of nickel carbonyl, urinary nickel increased in a few hours and reached a maximum about the fourth day, returning to normal in 10 to 14 days. Although an increase of urinary nickel gives an indication of nickel carbonyl absorption, clinical signs and symptoms remain the best guide of the severity of poisoning.

The carbonyl process for the production of pure nickel was discovered by Langer and Quincke in 1889. In recent years the uses of nickel carbonyl gas have extended to the manufacture of acrylic esters, catalysts and to the splitting of oils.

One of the main difficulties when dealing with nickel carbonyl poisoning is the existence of both an immediate and a delayed reaction. Clinical symptoms and a knowledge of the nickel content of the blood and urine help to establish the diagnosis. An increase of nickel in the urine furnishes proof of absorption, but no quantitative relationship to clinical symptoms has been established.

Former methods of urine analysis were too complex to be of practical value. The simplified method now described makes use of the fact that dimethylglyoxime precipitates nickel in neutral or ammoniacal solutions; this precipitate is so soluble in chloroform that small amounts of nickel can be completely extracted from aqueous solutions. This chloroform extract, when treated with hydrochloric acid returns the nickel to the aqueous phase where it can be determined colorimetrically. The method is a modified form of that described by Sandell (1944).

Method

Reagents Required:

(*a*) *Ammonium citrate solution.*—500 ml. ammonium hydroxide (S.G. 0·88) is added to 500 g. citric acid until solution is complete, and made up to one litre with water.

(*b*) *Ammoniacal dimethylgloxime.*—1 g. dimethylglyoxime is dissolved in 500 ml. of ammonium hydroxide (S.G. 0·88) and made up to 1 litre with distilled water.

(*c*) *N*/10 *iodine solution.*—Weigh out 12·7 g. powdered purest resublimed iodine into a litre flask. Add 20 g. of pure potassium iodide and 200 ml. water; shake until the iodine is dissolved. Make up to a litre. Keep well stoppered and in the dark.

(*d*) *Ammonia.*—(i) Concentrated ammonia (S.G. 0·88), (ii) 28% ammonia.

(*e*) *Concentrated hydrochloric acid.*

(*f*) *N*/10 *hydrochloric acid.*

(*g*) *Bromine water.*

(*h*) *Nickel.*—Standard solution—1·137 g. $NiSO_4 6H_2O$ (22·3% nickel) per 2½ litres equivalent to 100 mg./l. or 100 p.p.m.

(*i*) *Calcium acetate solution*—44 g./l.

Short range *p*H papers are used for *p*H determinations.

Method:

(1) *Removal of Phosphates.*—Nickel is incompletely recovered from urine when phosphates are present. Removal of phosphates by the method suggested by Darbey (1952) allows complete recovery of added nickel.

Take 50 ml. of urine, add 1·5 ml. of calcium acetate solution and 5 ml. ammonia (28%). Shake, allow to stand for five minutes, then filter. This separates the phosphates.

(2) *Destruction of Chelate.*—When calcium disodium versenate and potassium dithio-oxalate C.P., have been used for the treatment of nickel carbonyl poisoning, the urinary nickel must be released from the chelate complex before estimation.

Make the filtrate from (1) above, *p*H 1 with HCl, allow it to stand for about 10 min.; this releases the nickel from the chelate complex.

(3) *Extraction of Nickel.*—Make ammoniacal with concentrated ammonia to about *p*H 8; add 2 ml. of ammoniacal dimethyglyoxime and shake for two minutes,

then add 2 ml. chloroform and repeat shaking. Allow to stand, then run off chloroform layer into centrifuge tube.

Centrifuge: Remove any urine remaining on top of the chloroform layer, using a suction apparatus. Repeat the chloroform extraction and add this extract to previous extraction.

Shake the chloroform extract with about 1 ml. N/10 HCl, making certain the solution is acid, and centrifuge. Remove the top acid layer to a separate tube; repeat this process adding the second acid layer to the previous one.

To this acid solution is now added one drop of N/10 iodine. At this stage a few drops of ammonium citrate solution are added to prevent interference by iron, as shown in Table 1. If the iron is complexed with citrate, interference is prevented and a correct estimation of nickel is made.

TABLE 1

THE EFFECT OF IRON ON NICKEL ESTIMATIONS AND ITS PREVENTION BY THE ADDITION OF AMMONIUM CITRATE

Iron Added (mg.)	Ammonium Citrate Solution (ml.)	Nickel Added (mg.)	Nickel Found (mg.)
0·008	—	0·005	0·0058
0·016	—	0·005	0·0062
0·032	—	0·005	0·0070
0·4	—	0·005	0·0072
0·008	0·5	0·005	0·0049
0·016	0·5	0·005	0·0051
0·032	0·5	0·005	0·005
0·4	0·5	0·005	0·0047

Decolourize with concentrated ammonia to *p*H 9.

Add about 1 ml. of ammoniacal dimethylgloxime, shake, cool, then make up to 5 ml. If the solution is turbid, filter. If nickel is present the colour intensity increases slowly with time so that readings should be made within 15 minutes.

Measurements are made with a Hilger absorptiometer using a Kodak 1 filter with a tungsten filament lamp. As the effective band width of light is considerable, the calibration graph is slightly curved.

Nickel Content in Human Urine

Persons Not Engaged in the Nickel Industry.—Nickel is present in almost all foods and after digestion is eventually excreted in the urine.

In some countries nickel utensils are widely used for cooking and various investigations have been carried out to determine whether the amounts of nickel absorbed could give rise to toxic symptoms. Drinker, Fairhall, Ray, and Drinker (1924) concluded that the maximum concentrations of nickel found in the urine in these circumstances were too low to be a possible source of kidney damage.

For the nickel content of the urine of people not concerned in any way with the nickel industry, Ghiringhelli and Dakli (1956) give a figure of 0·03-0·09 p.p.m. with a mean of 0·05. Sorinson, Kornilova, and Arteńeva (1958) report a figure of between 0·03 and 0·1 p.p.m. Kincaid, Stanley, Beckworth, and Sunderman (1956) record a group of 69 unexposed persons with a value of 0·011 p.p.m. (S.D. ± 0·009). From these data it may be concluded that only one specimen in 50 selected from a normal population will be found to exceed a value for nickel in urine of 0·03 p.p.m. and this has, therefore, been selected as the upper limit of normal.

Tompsett and Fitzpatrick (1950), whilst estimating the amounts of metal in the urines of shipbreakers and others not engaged in this industry, found an average of 0·029 p.p.m. nickel in the urine, and 8·3 mg. nickel per 100 g. dried faeces.

I estimated the nickel content in the urines of applicants for employment aged 18 to 48 and found the average to be 0·04 p.p.m. with a standard deviation of ± 0·02.

Persons Engaged in the Nickel Industry.—Ghiringhelli and Dakli (1956) noted that the average nickel content in the urines of 14 men, who had worked near nickel carbonyl for 180 days before scrupulous observance of safety arrangements on the part of the personnel engaged, was 0·365 p.p.m. When the safety arrangements were more strictly observed, the average fell to 0·276 p.p.m.

Sorinson *et al.* (1958) determined the nickel concentration in the blood and urine of 62 workers before and after one and a half years' work in a new plant using nickel carbonyl. Urine values of 0·67, 0·8 or even 1·78 p.p.m. were reached, representing an increase several times above the upper limit of normal. These high values of nickel in urine were only found in workers in the principal production departments. No toxic effects were observed. In workers employed in ancillary departments, the nickel content in urine did not exceed 0·05 p.p.m.

Sorinson *et al.* also noted that the nickel content in urine increased by 0·094 p.p.m. by the end of the shift. They concluded that frequent determinations of nickel in urine should be made in order to reduce the health hazards in all departments of nickel carbonyl production.

I have carried out periodic medical examinations of all men employed in the industry with special regard to the nickel content of their urines. The following results give the average amounts of nickel found in the urine of men working in the various processes: (*a*) Men engaged in departments where nickel carbonyl is produced and used—between 0·008 and 0·15 p.p.m. was found; (*b*) Men in departments where no carbonyl is produced or used but where the raw material is smelted or chemically precipitated: (i) Furnaces—between 0·01 and 0·043 p.p.m., (ii) Chemical precipitation plants—between 0·005 and 0·06 p.p.m., (iii) Calcination plant—between 0·002 and 0·05 p.p.m.

Inhalation of Nickel Carbonyl.—After the inhalation of nickel carbonyl gas, nickel soon appears in the blood and later in the urine and faeces. Bayer (1939) found 52 and 400 micrograms of nickel respectively in the bladder urine of two men who had died a few days after poisoning. In another case Bayer found 3·9 p.p.m., and in a fatal case 0·13 p.p.m. Sunderman and Kincaid (1954) state that the average concentration in 13 cases of poisoning on the fifth day after exposure was 0·17 p.p.m. They also reported on 36 persons accidentally exposed to the vapours of nickel carbonyl, of whom two died and many were critically ill. The nickel concentrations in urine and blood were increased many times above normal after exposure.

Tedeschi and Sunderman (1957) carried out nickel balance studies on normal dogs. These showed that 90% of the ingested nickel was excreted in the faeces and 10% in the urine. After exposure to the vapours of nickel carbonyl, the amount of nickel excreted in the urine was strikingly increased. No such increase was found in the faeces.

In rabbits exposed to nickel carbonyl, Armit (1907) found that 75% of the nickel was excreted in the urine. The rate of elimination was irregular, and reached its maximum on the fourth or fifth day.

Sorinson (1957) reports that a patient undergoing a routine examination showed a normal nickel content of 0·11 mg./100 ml. in blood and 0·036 p.p.m. in urine the day before an accident. On the third day after exposure, there was 0·82 mg./100 ml. in blood and 1 p.p.m. in urine.

Sorinson *et al.* (1958) report that the nickel content in urine in cases of acute poisoning during the first three days varied from 0·14-1·023 p.p.m.

In cases of nickel carbonyl poisoning, Ceresa (1947) found that nickel was present in the urine after 24 hours, then diminished until the fourth day, started to rise on the fifth day, but returned to normal on the eighth day.

Men under my care who are working on the production of carbonyl have been instructed that if they suffer from a headache or think that they have been exposed to the gas, they must report immediately to the medical department for precautionary treatment. They are put to bed and oxygen therapy is started. Samples of blood are taken for the nickel and carbon monoxide content, and urine samples are taken later. These figures are compared with the amount found during routine examinations; an increase, together with clinical signs and symptoms indicates inhalation of the gas.

Data from 23 cases of accidental exposure are presented in Tables 2 and 3.

TABLE 2

NICKEL IN URINE AFTER INHALATION OF NICKEL CARBONYL (MEN WHO DID NOT REPORT IMMEDIATELY AND WHO LOST TIME)

Case No.	Pre-accident Content (p.p.m.)	Parts per Million (after Accident)											
		1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day	8th Day	9th Day	10th Day	11th Day	12th Day
*1	0·09	—	—	0·9	2·0	—	0·8	0·4	0·7	0·5	0·6	0·16	0·16
*2	0·1	—	—	0·7	0·7	0·7	0·8	0·6	0·6	0·5	0·4	0·29	0·36
3	—	—	—	—	1·2	—	—	1·8	—	—	—	—	—
4	0·09	—	—	—	1·4	1·1	0·9	0·8	0·6	0·4	0·4	0·5	0·16
5	0·4	—	—	—	0·4	0·4	0·4	0·2	0·3	0·4	0·2	0·4	0·2
6	0·09	—	—	0·48	—	0·8	0·7	0·6	0·7	0·6	0·4	0·4	0·2
*7	0·4	—	—	1·4	0·5	—	—	—	—	—	—	—	—
8	0·65	—	—	—	1·4	1·2	1·2	—	—	—	—	—	—
*9	0·98	—	—	2·8	—	—	2·0	—	0·9	—	—	—	—
10	—	—	—	—	—	—	0·28	—	0·2	—	—	—	—
11	0·4	—	—	—	1·1	—	1·4	1·0	—	—	—	—	—
12	—	—	—	—	—	0·7	—	—	0·4	—	—	—	—
13	0·1	—	—	—	0·8	0·9	0·8	0·6	0·6	—	—	—	—
14	0·75	—	—	0·55	0·7	0·7	—	—	0·8	—	—	—	—
15	—	—	1·0	0·6	1·4	1·2	0·7	—	—	—	—	—	—

*Admitted to hospital.

Case No. 1.—In hospital for seven days; temperature 101° for four days returning to normal from the fifth day. Pulse varied between 110 per min. and 70 per min. Respirations varied from 35 per min. to 25 per min. returning to normal by the seventh day. Pulse respiration ratio 1 : 3 to 1 : 4. Blood pressure 130/80. Urine output averaged 30 oz. daily for first few days, then 60 oz. daily by discharge date. Uneventful recovery.

Case No. 2.—In hospital for six days. Temperature varied from 103°-100° returning to normal on sixth day. Pulse varied from 130-90 per min. returning to 70 on the sixth day. Respirations varied between 52-30 per min., returning to normal on the sixth day. Pulse respiration ratio 1 : 2 to 1 : 3. Blood pressure 150/100, falling to 120/90 by the third day. Uneventful recovery.

Case No. 7.—In hospital for seven days. Temperature 102° for three days returning to normal on the sixth day. Pulse varied from 135 to 90 per min. for four days, returning to normal on the fifth day. Respirations 45 per min. for four days, then returned to normal. Pulse respiration ratio 1 : 3 to 1 : 4. Blood pressure 148/90. Urine output averaged 30 oz. daily for first five days then 55 oz. daily. Dyspnoea on exertion for about one month, then full recovery.

Case No. 9.—In hospital for seven days. Temperature 103° returning to normal on the fourth day. Pulse 120 per min. for two days, 100 per min. for two days, then normal. Respirations varied between 35-25 for five days then returned to normal. Pulse respiration ratio 1 : 3+. Urine output averaged 52 oz. daily for first two days, then 36 oz. for one day only, then returned to 64 oz. daily.

Two 0·5 g. calcium disodium versenate tablets were given daily to each of the above men for four days, commencing three days after the inhalation.

TABLE 3

NICKEL IN URINE AFTER INHALATION OF NICKEL CARBONYL (MEN WHO REPORTED IMMEDIATELY AND WHO LOST NO TIME)

Case No.	Pre-accident Content (p.p.m.)	Parts per Million (after Accident)											
		1st Day	2nd Day	3rd Day	4th Day	5th Day	6th Day	7th Day	8th Day	9th Day	10th Day	11th Day	12th Day
16	—	1·0	1·2	—	—	—	0·2	0·15	0·2	0·2	—	—	—
17	—	0·38	2·0	—	—	—	0·3	0·4	0·2	0·2	—	—	—
18	—	0·1	0·2	—	—	—	0·2	0·2	0·15	0·2	—	—	—
19	0·11	0·3	—	—	—	—	0·4	0·5	0·9	0·9	—	—	—
20	—	0·4	—	—	—	—	—	—	—	—	—	—	—
21	—	1·3	2·9	—	—	—	0·8	0·8	0·8	1·0	—	—	—
22	—	0·8	1·4	—	—	—	0·4	—	—	—	—	—	—
23	—	0·7	—	—	—	—	—	—	0·2	—	—	—	—

Two 0·5 g. tablets of calcium disodium versenate were given daily for two days to each of the above men.

These Tables show that an increase of nickel occurs in the urine a few hours after inhalation and increases until it reaches its maximum about the fourth day, gradually diminishing until it returns to normal about the 10th to 14th day.

An increase of nickel in the urine can only be used as an indication of nickel carbonyl poisoning and not as a measure of the severity of the case. Clinical signs and symptoms are the best guide to severity.

I should like to express my thanks to my staff for their help in this work.

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CLINICAL, BRONCHOGRAPHIC, RADIOLOGICAL AND PHYSIOLOGICAL OBSERVATIONS IN TEN CASES OF ASBESTOSIS

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(RECEIVED FOR PUBLICATION JUNE 20, 1959)

Ten cases of asbestosis (eight male, two female), aged 45-65 years have been kept under observation for periods of up to eight years. Bronchiectasis was demonstrated bronchographically in six cases. Clubbing of the fingers and coarse crepitations appeared to be signs of bronchiectasis rather than of uncomplicated asbestosis. It is suggested that the prevalence of bronchiectasis is higher than has been reported previously because the patients survived longer. The radiological findings are tabulated and compared with previous descriptions. In these subjects there was no relationship between radiological and clinical state. Nine patients eventually showed clinical deterioration and it often proceeded rapidly. The radiograph however, usually remained unaltered.

Pulmonary function tests, including diffusing capacity, arterial blood analysis and estimation of mechanical properties of the lung, were carried out in these 10 cases, and in 11 asbestos workers (aged 35-64 years) without radiological abnormality. The steady state diffusing capacity for carbon monoxide (Dco) at rest was lower in asbestosis than in the control subjects. The pulmonary compliance was remarkably low in asbestosis and related fairly closely to the vital capacity. The maximum voluntary ventilation was also low and was related to increased pulmonary resistance but it cannot be said whether this is in the airways or in the lung tissue. Indirect evidence of inequalities of ventilation/perfusion ratio was obtained in most cases. There is no convincing evidence that pulmonary fibrosis occurs without radiological abnormality, but a defect of diffusion may occur. There is no test of pulmonary function which is diagnostic, but a low pulmonary compliance, especially if combined with a low diffusing capacity, is confirmatory.

It is suggested that the demonstration of a progressive decline in vital capacity, or in diffusing capacity, may enable a diagnosis of asbestosis to be made before radiological abnormality has appeared, but this point has not been proved.

PART 1: CLINICAL AND RADIOLOGICAL FINDINGS

Two features ascribed to asbestosis are the occurrence of distinctive râles at the lung bases, and of clubbing of the fingers. Observers differ, however, in their descriptions of the type of râles present and in the frequency with which they have seen clubbing. Oliver (1927), describes "tinkling moist sounds" or "moist râles" and Haddow (1929) states that "moist râles and crepitations" were present during the winter months in his four cases. Hunter (1957) refers to "medium, crepitant râles, often with a metallic tone" but adds that these were sometimes absent. Wood (1929) however, mentions adventitious sounds which have "a dry crackling quality", while Wood and Gloyne (1930) in their review of 100 cases describe "fine dry crackles not dissimilar to those often heard over the bases of emphysematous lungs", and to "more superficial crackles produced by movements of a damaged pleura... mingled with the fibrotic râles". Merewether (1930) records "pleural crepitations" and scattered fine râles in some, but not all, cases, but he regards these as of little diagnostic value. Johnstone (1948) states that "fine, crackling râles" appear as the disease advances and Wyers (1949) says that "dry, crackling sounds can generally be heard" but are evanescent.

It would be possible to give details of a similar disagreement among these authors concerning the

frequency with which clubbing of the fingers is seen. Suffice it to say that Merewether (1930) found it in only a few of his 95 cases, Wyers (1949) in 55%, while Meiklejohn (1956) states that it is almost pathognomonic of the disease.

The disagreement among these authors about the importance of clubbing and on whether crepitations occur and, if so, whether they are moist or dry, is of little importance in the recognition of the disease because the diagnosis is, nowadays, based mainly on radiography. However, the differences in their opinions suggest that they may, in fact, be describing different aspects or stages of the disease. The disease may vary from place to place according to the type of fibre which has been inhaled (for "asbestos" is a name for a group of fibrous minerals with diverse physical and chemical properties), or as Wyers (1949) believed, the disease may have altered over the course of the 60 years for which it has been known.

This paper presents evidence, albeit from a small group of patients, that differences in the physical signs indicate identifiable differences in the state of the lungs, and strongly suggests that the character of the disease has changed since the classic descriptions of 30 years ago. In view of this the radiological findings are reported in detail for comparison with classical descriptions. This work does not provide sufficient evidence to assign different roles to the different types of asbestos. All the subjects were exposed to both chrysotile and amosite fibres.

Clinical Material and Investigation

The cases described below are 10 patients (eight male, two female) who were referred to the department on account of respiratory symptoms, or an abnormality discovered by mass radiography. In all cases the diagnosis was made on a combination of typical radiological changes (assessed by three independent observers) and a history of exposure to asbestos. The patients have been kept under observation for up to eight years. The physical signs in these patients are contrasted with those found in 11 insulators (laggers) whose radiographs were considered by three independent observers to be normal. All these men were examined specially for the purposes of this paper and only one had respiratory symptoms. In order to avoid the dangers of selection (Carpenter, Cochrane, Gilson, and Higgins, 1956) all the men employed as laggers by a certain industry were examined, but the findings in three men have been excluded: two had histories of prolonged exposure to coal and silica dust in other industries with under two years exposure to asbestos, and one had apical tuberculosis. Detailed occupational histories of the patients and of the control subjects are given in Appendix 1. It will be seen that six of the patients with asbestosis had done work which was identical with that done by the healthy control subjects.

Routine clinical examination and antero-posterior radiography was carried out on all subjects. The sputum of all patients was examined repeatedly for asbestos bodies and tubercle bacilli. The latter were never found. Bronchography was performed in the 10 cases of asbestosis. In four cases bronchography was restricted to one lung because of severe dyspnoea. The side chosen for investigation was that which showed the most abnormal signs, and in two of these four cases bronchiectasis was demonstrated there. It must be stressed that the absence of bronchiectasis in the other two cases has not been firmly established, while in the remaining six cases the extent of the bronchiectasis has not been fully explored.

Pulmonary function tests were also carried out on all subjects and are described in Part 2 of this paper. The clinical and radiological findings which are given in Tables 1 and 4 are discussed below. The clinical findings altered with the years, and the findings given in Table 1 are those at the time the bronchogram was done. The bronchogram was assessed by two independent observers who were unaware of the clinical findings.

In Table 2 these findings are summarized and compared with the signs and symptoms in 11 asbestos workers without radiological abnormality.

Results

It will be seen, from Table 2, that clubbing of the fingers and the presence of crepitations in the lungs were exclusive features of the patients with asbestosis but that neither of these was present in all of them. The crepitations have been divided into "fine" (which is probably the same as "dry"), and "coarse". Fine crepitations are similar to those which are heard transitorily at the lung bases in elderly bedridden patients without lung disease. Coarse crepitations are those which have a moist or bubbling character, often accompanied by musical squeaks or tinkling sounds, and resemble those commonly heard in bronchiectasis. Fine crepitations were heard in two patients and coarse ones in eight. Cyanosis and dyspnoea were much commoner, and reduced chest expansion somewhat commoner, in the patients with asbestosis. The cyanosis was seldom accompanied by significant arterial desaturation (see Part 2) and this suggests that peripheral blood flow may be reduced. Stone (1940) stressed the cardiac effects of the disease.

TABLE 1

PHYSICAL SIGNS AND BRONCHOGRAPHY IN ASBESTOSIS

Case No.	Age (Yrs.)	Sex	Date of Examination	Cyanosis	Clubbing	Chest Expansion	Crepitations	Asbestos Bodies	Bronchogram	Dyspnoea
1	65	M	11.11.58	+ +	+ +	Reduced	Widespread, coarse, both bases	Present	Saccular and cylindrical bronchiectasis right middle and lower lobes U	5
2	63	M	2. 9.56	+	+ +	Reduced	Widespread, coarse, both bases	Present	Cylindrical apical segment of right lower lobe, saccular at base U	3
3	60	M	17.11.58	+	+	Reduced	Widespread, coarse, both bases	Absent	Cylindrical bronchiectasis both lower lobes and right middle lobe B	3·5
4	55	M	6. 1.59	+	0	No expansion	No crepitations	Present	Normal bronchi right lung U	4
5	54	M	13.12.58	+ On exercise	0	Reduced	Few, coarse, lower part of left axilla. Fine at both bases	Present	Normal bronchi both lungs B	3·5
6	53	M	19.12.58	+ On exercise	0	Reduced	Few, coarse, lower part of left axilla especially	Present	Normal bronchi both lungs B	3
7	54	M	8. 1.59	+	+	Normal	Fine crepitations lower part of right axilla	Absent	Normal bronchi right lung U	3·5
8	52	M	13. 1.59	0	±	Normal	Few, coarse, both axillae. Widespread fine crepitations both bases	Present	Cylindrical bronchiectasis L. lingula and both bases B	3
9	52	F	8.12.58	+	+ +	Reduced	Coarse, left base, and right base	Unknown (records lost)	Saccular and cylindrical bronchiectasis left lower lobe and lingula B	3
10	48	F	2. 2.59	0	0	Reduced	Coarse crepitations both bases	Present	Cylindrical both lower lobes and in lingula B	3

0 = Absent.
± = Doubtful.
+ = Present.
+ + = Well marked.

Bronchogram U = Unilateral.
B = Bilateral.

Dyspnoea 2 = No symptoms on flat but slow on hills.
3 = Can walk 1 mile or more at own pace on flat.
3·5 = Can walk 400 yards on flat at own pace.
4 = Can walk 100 yards on flat.
5 = Breathless washing, dressing and talking.

TABLE 2

PHYSICAL SIGNS IN ASBESTOS WORKERS

	Radiologically Normal	Radiological Asbestosis
Number	11	10
Clubbing	0	6
Coarse crepitations	0	8
Reduced chest expansion	3	8
Cyanosis	2	8
Dyspnoea* (mean intensity)	0·6	3·5

*Assessed numerically as in Table 1.

TABLE 3

SIGNS OF BRONCHIECTASIS IN 10 CASES OF ASBESTOSIS

	Asbestosis and Bronchiectasis	Asbestosis Only
Number	6	4
Clubbing	5	1
Coarse crepitations	6	2 (localized)
Reduced chest expansion	5	3
Cyanosis	4	2 (+ 2 on exercise)
Dyspnoea* (mean intensity)	3·5	3·5
Bronchogram	Bronchiectasis	No bronchiectasis

*Assessed numerically as in Table 1.

The results of bronchography are given in Table 1. There was cylindrical bronchiectasis in six patients and saccular bronchiectasis was present as well in three. This was usually seen in the lower or middle lobes but no effort was made to define its total extent, and it may have been more widespread. In Table 3 the clinical signs demonstrated in the six patients with bronchiectasis are compared with those found in the four without bronchiectasis. Though the numbers are very small for generalization it appears that clubbing of the fingers and widespread coarse crepitations usually accompany bronchiectasis and are seldom seen in its absence.* A similar conclusion was reached by Stone (1940) who writes "Moist râles were found only when there was definite evidence of associated bronchitis or bronchiectasis".

Among the patients without bronchiectasis the one in whom there was clubbing did not have a bilateral bronchogram. The two in whom coarse crepitations were heard had normal bronchograms on both sides, but the region in which these crepitations were heard was limited to an area about the size of a penny in the lower axillary region and it is possible that very limited bronchiectasis was present in these cases also. Cyanosis at rest was slightly commoner in the cases with bronchiectasis, but there was no evidence that the presence of bronchiectasis increased the intensity of dyspnoea.

Radiology.—The radiological findings are given in Table 4 together with the findings at an earlier date. The radiographs have been classified into

*Since this paper was written a further case of asbestosis with bronchiectasis has been seen. In this patient there were fine crepitations, but neither coarse crepitations nor clubbing of the fingers were present.

TABLE 4

RADIOLOGICAL FINDINGS IN 10 CASES OF ASBESTOSIS

Case No.	Age (Yrs.)	Sex	Date of Chest Radiograph	Dust Exposure (in Years)	Miliary Mottling	Ground Glass	Streaking	Hilar Enlargement	Shaggy Heart	Pleural Thickening	Apical Translucency	Other Abnormalities	Radiological Stage	Dyspnoea
1	57	M	29. 3.51	31	+	0	0	0	0	0	0	Cystic appearance at bases first seen 1956	0	2
	65		11.11.58	33	+	0	+ +	+ +	+ +	0	0		III	5
2	62	M	22. 6.55	28	+ +	0	+	+	0	+	+	—	II	2
	65		23. 7.58	28	+ +	0	+	+	0	+	+		II	3
3	53	M	19.10.51	26	+ +	0	+	+	0	+	0	—	II	1
	60		19.12.58	27	+ +	0	+	+	0	+	0		II	3·5
4	47	M	17. 5.51	33	0	+	+ +	+	0	0	+	—	II	1
	55		1. 9.59	36	0	+	+ +	+	0	0	+		II	4
5	50	M	2.12.54	32	+	0	+	+	0	0	0	—	II	2
	54		13.12.58	36	+	0	+	+	0	0	0		II	3·5
6	53	M	4.12.57	17	+ +	0	0	0	0	+	0	Radiograph of shoulder 1954 showed abnormal lung	I	3
	54		19.12.58	17	+ +	0	0	0	0	+	0		I	3
7	49	M	17. 2.54	27	0	+	+	+	0	0	0	—	II	2
	53		12. 3.58	27	0	+	+	+	0	0	0		II	3·5
8	51	M	30. 1.58	11	0	0	+ +	+ +	0	0	0	Cystic appearance at left base	II	3
	52		4.12.58	11	0	0	+ +	+ +	0	0	0		II	3
9	45	F	24.10.51	11	0	0	+	+	0	0	0	Healed apical lesion on right. Cystic appearance, left base first seen 1957	II	2
	52		28. 2.58	11	0	0	+	+ +	+	+	0		III	3
10	46	F	8. 2.57	20	0	+	+	+	0	+ + *	0	—	II	3·5
	48		9.10.58	20	0	+	+	+	0	+ +	0		II	3
Totals					5	3	9	9	2	5	2			

three stages. The presence of hilar enlargement distinguishes stage II from stage I, while loss of cardiac outline indicates stage III. This classification is in line with the schemes proposed by Twining (quoted by Merewether, 1930), Saupe (quoted by Wegelius, 1947), Bristol (1955) and Gaffuri and Berra (1957).

Seven abnormalities could be recognized in the radiographs of these 10 patients.

(1) Pinpoint miliary mottling, indistinguishable from pneumoconiosis of coal-miners.

(2) A "ground glass" homogeneous veiling of the middle third of the lung fields, resembling breast shadowing in quality, but not in extent.

(3) Accentuation of lung markings, producing coarse streaks, which criss-cross to give the appearance of a wide-mesh net. This is most obvious near the hilum but spreads towards the periphery.

These three changes are all most obvious in the middle third of the lung.

(4) Enlargement and shagginess of the hilar shadows, apparently due to fibrosis.

(5) A shaggy and indefinite outline to the heart.

(6) Pleural thickening in the costo-phrenic angles.

(7) Translucency of one or both upper lung fields.

These abnormalities were not all present in each case and there is no abnormality which occurs in every one. It therefore seems probable that the type of radiological abnormality which was first to appear varied from case to case. Alteration of the radiographs with time occurred in only two patients, one of whom *was* and the other *was not* exposed to asbestos during the interval.

Discussion

Clinical Signs and Bronchiectasis.—These 10 cases of asbestosis have, between them, shown all the clinical signs mentioned by previous authors with the single exception of dullness to percussion which was not noted in any of them. The finding of coarse crepitations and of clubbing of the fingers suggested the presence of bronchiectasis, which was unusually common in this group of patients. Published reports of its prevalence are based on post-mortem studies; the only previous reference to bronchography is the single case in whom Gernez-Rieux, Balgairies, and Claeys (1954) demonstrated chronic bronchitis. Bronchiectasis was first demonstrated by Stewart in 1929 (see Merewether, 1930) but in 1927 Oliver had interpreted the presence of "tinkling moist sounds" as evidence of cavitation, and Haddow (1929) had reported radiological evidence of basal cavities (possibly bronchiectatic). Post-mortem evidence of bronchiectasis was also noted by Wood and Gloyne (1930) and in a dog, as well as in human cases, by Gloyne (1933). Though recognized as a complication by nearly all subsequent writers it has never been regarded as common. Wyers (1949), for example, in a discussion of bronchiectasis among his 115 fatal cases wrote "Only three undoubted cases occurred in the present series and one of these was a congenital condition affecting the apex".

There are three possible explanations for the high proportion of bronchiectasis in the present series: bronchiectasis may be more readily recognized from a bronchogram during life than at autopsy; selection of the cases may have exaggerated its prevalence; bronchiectasis may be commoner now than formerly. It is

reasonable to suppose that cylindrical bronchiectasis might sometimes have passed unnoticed at autopsy, since the lungs were not inflated and fixed before section. If the association between clubbing and bronchiectasis is accepted, then errors at autopsy must account for all the difference between bronchographic and autopsy frequency of bronchiectasis, at any rate in the later papers in which clubbing was noted in more than half the patients. This seems unlikely, but there is nothing to support the suggestion that patients with bronchiectasis are more prone to seek hospital treatment than other patients with asbestosis. On the average, dyspnoea in patients with bronchiectasis was no more severe than in those without it. Cough, also, was much the same in both types of patient (the autopsy reports have usually been of dry bronchiectasis (see Gloyne, 1933)), and was productive in only two of the cases with bronchiectasis. In one of the cases with bronchiectasis (Case 3), who was referred after mass radiography, the presenting symptom was not respiratory and in this and one other, coarse crepitations, which appear to indicate the presence of bronchiectasis, were not present when they first attended, but appeared one and seven years later. This last observation suggests that bronchiectasis may be, as Stone (1940) implied, a late complication of asbestosis. If this is so, then an increase in the frequency with which bronchiectasis is observed could be the result of the longer survival of patients with asbestosis in recent years. Both Wyers (1949) and Knox (1959) have noted slower development of fibrosis and longer survival.

It is concluded, therefore, that bronchiectasis as a complication of asbestosis not only occurs more frequently than it used to, but also is more common than past necropsies have suggested.

The question of whether bronchiectasis is secondary to asbestosis, or is an incidental disease occurring in those patients who have been examined, has been partly answered by the evidence in the preceding paragraphs. The conclusion that it is secondary to asbestosis is supported by the observation that, in two cases, radiographic evidence of cystic changes in the lungs appeared after the diagnosis of asbestosis had been made (Table 4) and that in several instances the patients with bronchiectasis had been capable athletes in their youth.

Radiology.—All the seven abnormalities seen in the radiographs of these 10 cases were described in 1929 by Wood and by Haddow. Early writers, however, did not distinguish clearly between miliary mottling and the "ground glass" appearance. Massive shadows, which were present in some of Wood's cases, were not seen in the present series, and pleural thickening was less evident. Otherwise this study shows no evidence of change in the radiographic appearances of this disease in the last 30 years. The frequency with which pleural thickening or apical translucency occurred was very similar to that reported by Wegelius in 1947.

Lack of correlation between radiological and clinical state has been reported by Lanza, McConnell, and Fennel (1935), Wright (1955), Amsler (1958) and by many other authors and is confirmed by the present series of cases. The clinical condition deteriorated in nine cases while the radiological stage altered in only two. Thus the patient's account of his symptoms gives a clearer picture of his disability than does the radiograph of his chest.

Progression of the Disease.—Serial observations on patients with asbestosis have seldom been reported in the literature. Wegelius (1947) reported 37 examples of radiological deterioration, mainly in the earliest stages, during two to three years' observation of 126 cases still exposed to asbestos dust. Stone (1940) saw progression in only two of 13 cases (both in Stage III) followed for the same time unexposed to the dust. Whether there is radiological progression or not there is general agreement that clinical deterioration is usual. Smith (1955), however, believes that the disease will not progress after exposure ceases.

In our series all cases, except Case 10, deteriorated during one to eight years of observation. Case 5 remained in the same work throughout the period of observation (at his own request) and Cases 1, 3, and 4 were exposed for two, one, and three years, respectively, after the first examination. The remaining five cases deteriorated despite removal from contact with asbestos dust, while in Cases 3 and 4 the clinical state did not worsen until after exposure ceased. The clinical course varied greatly from case to case. Case 4 showed no change between 1951 and 1954 while Case 3 remained virtually unaltered from 1951 to 1957 and Cases 5 and 7 did not alter for two years. Cases 2 and 8, on the other hand, showed obvious decline in one year and, in all cases, once deterioration set in, it advanced rapidly. Evidence of heart failure appeared in only one case, Case 4, who developed oedema in 1958, seven years after the diagnosis was made.

These observations confirm that by the time that radiological abnormalities have developed the disease has already entered a progressive phase. Though deterioration may not be noticed if the follow-up is short it appears to be inevitable, despite removal from further exposure to the dust. This emphasizes the importance of taking every possible step to prevent the disease from occurring.

PART 2: PULMONARY FUNCTION TESTS IN 10 CASES OF ASBESTOSIS AND IN 11 NORMAL ASBESTOS WORKERS

It is suggested in Part 1 of this paper that asbestosis has already entered a phase of pro-

gressive deterioration by the time that radiological abnormalities are present. The evident need for a method of making the diagnosis at an earlier stage has prompted the search for specific changes in pulmonary function. The results of function tests in 10 cases of asbestosis and in 11 controls are described in Part 2 and the literature is briefly reviewed.

Wood (1929) recorded a low vital capacity in one case of asbestosis, and Stone (1940) confirmed this in 13 cases, but the first detailed study of the function changes in this disease was that of Roemheld, Kempf, and Wedler (1940). Their 19 patients with asbestosis showed an increased frequency of respiration at rest, restriction of maximum ventilation, and reduction of vital capacity, of which the last was roughly related to the severity of the radiological abnormality. Baldwin, Cournand, and Richards (1949) added the observation that the arterial saturation was low in one case and fell further on exertion. They included this case amongst others showing alveolo-respiratory insufficiency where the presence of a diffusion defect had been deduced. Bastenier, Denolin, de Coster, Cammaerts, and Denolin-Reubens (1952) and Gernez-Rieux *et al.* (1954) confirmed that exercise induced a fall of arterial saturation in four more cases. Bastenier, Denolin, de Coster and Englert (1955) reported observations on a further eight cases. Maximum voluntary ventilation, vital capacity, total lung volume, mixing efficiency and arterial saturation at rest were all reduced; physiological dead space was an increased fraction of the tidal air in the four cases in whom this was measured. There was no relationship between the radiological picture and the type or degree of pulmonary insufficiency and they concluded: "Il n'y a pas de tableau fixe ou définitif de l'état fonctionelle dans cette affection pulmonaire".

Wright (1955) referred to "the relatively stiff and uncompliant lung of the asbestotic" but it is not clear whether the compliance had actually been measured. Wright gave very few details about his 57 cases but he stated that there is an increased alveolo-arterial gradient for oxygen which "clearly indicates an impediment to the passage of oxygen across the membrane separating the gas from the blood phase in the lung". The high alveolo-arterial gradient for oxygen could, however, have been due to inequalities of ventilation/perfusion ratio, and the diffusing capacity does not appear to have been measured. Wright confirmed the reduction of vital capacity and total lung volume but found little or no impairment of maximum breathing capacity. He agreed with Bastenier *et al.* (1955) in concluding that the physiological state of these patients did not correlate closely with either their clinical or their radiological condition.

Gaffuri and Berra (1957) studied 30 cases by spirometry and demonstrated a clear relationship between functional and radiological abnormality. They found a reduction of vital capacity, of total lung volume, and of indirect maximum breathing capacity in the 20 cases who showed the more advanced radiological changes. They discuss the possibility of a diffusion defect which Champeix, Bodet, and Siboulet (1958) and Amsler (1958) consider to be present in all cases. Sartorelli (1957) added one more case in whom arterial saturation fell on exertion, and deduced a diffusion defect, but the only published measurements of diffusing capacity are those of Marks, Cugell, Cadigan, and Gaensler (1957), who found it to be about half normal in one case, and those of Bader, Bader, and Selikoff (1957) who reported a reduction in three out of five cases. Bader *et al.* (1957) also noted a fall in arterial saturation during exercise in some of their 18 cases.

Published observations on the mechanical properties of the lung are limited to one case, in whom Marshall and Dubois (1956) recorded a compliance which was about one third of normal.

It is clear therefore that further measurements of diffusing capacity and of lung mechanics are required; arterial carbon dioxide tension has been recorded in only seven cases and the possibility of inequalities of ventilation/perfusion ratio has been investigated in only nine. It was therefore decided that the 10 cases described in the first part of this paper should be investigated as thoroughly as possible, and the fact that they had been partially investigated a year or more previously (the pulmonary elastance in seven of these cases was detailed by Leathart in 1959) presented the opportunity of following the effect of time on the progression of some of the functional changes. Sartorelli (1957) is the only previous author to describe serial observations of pulmonary function.

All published work on the functional effects of asbestosis has lacked observations on a control group of subjects. Consequently it is an open question whether the reported changes were due to pulmonary fibrosis or to some other effect of working in a dust-laden atmosphere. It was therefore decided that this investigation should include a group of men who were working with asbestos but were free from clinical and radiological evidence of fibrosis.

Methods

The subjects were 10 patients with respiratory symptoms, all of whom had radiological signs of asbestosis.

The controls were 11 men employed as boiler-laggers, whose chest radiographs were all considered normal by three independent observers.

All subjects were seated when examined. In each the diffusing capacity of the lungs was estimated by a steady state method (Filley, MacIntosh, and Wright, 1954). These authors suggest that this method has an analytical error of about 25% but I find that two determinations in the same individual are usually within 15% of one another. Carbon monoxide concentration of inspired and of mixed expired air was estimated by infra-red absorption; duplicate analyses never differed by more than 1% of full scale deflection in the range 0·05 to 0·15%CO by volume. Duplicate analyses for oxygen and carbon dioxide, done with the Haldane apparatus, never differed by more than 0·1%. Arterial blood was collected anaerobically and oxygen saturation of blood and CO_2 content of plasma were estimated by the method of Courtice and Douglas (1947). The blood-gas analyses were done in duplicate and the difference between the two readings never exceeded 2%. The *p*H of whole blood was estimated at 38°C. and duplicate determinations differed by less than 0·05 units. CO_2 tension was calculated from the nomogram of Van Slyke and Sendroy (1928), with an estimated accuracy of ± 3 mm.Hg. Blood was kept in iced water between collection and analysis. In the controls, arterial saturation was estimated only when cyanosis was present. For the estimation of maximum voluntary ventilation (M.V.V.) expired air was collected, after instruction and practice, during three consecutive maximum ventilatory efforts, each of which lasted for 15 sec., and its volume was measured later. The rate of breathing was uncontrolled. Dynamic compliance and total non-elastic work of respiration were calculated from pressure-volume loops as previously described (Leathart, 1959); the standard error of the mean of repeated determinations of compliance was ± 5%, and of non-elastic work was ± 9%.

In the accompanying tables the diffusing capacity is given at S.T.P.D. but all other gas volumes are given at ambient temperature and pressure, saturated.

Results

The physiological findings are given in Tables 5 (asbestosis) and 6 (controls), and the chief differences are summarized in Table 7.

Dynamic Compliance and Vital Capacity.—In the patients with asbestosis the mean compliance was 0·046 l./cm.H_2O which is less than one fifth of the mean of 300 observations in normal subjects (0·214 l./cm.H_2O) which Leathart (1959) culled from the literature, and about half the lower limit of normal (0·091 l./cm.H_2O). In the laggers without radiological abnormality the mean compliance was 0·189 l./cm.H_2O. This difference is highly significant ($p<0·001$). The influence of age and of body-build on pulmonary compliance is doubtful (Leathart, 1959), but in any case the compliance in the patients with asbestosis is much too low, and the difference between them and the laggers is much too great to be explained in this way.

In these experiments the compliance was measured

TABLE 5

LUNG FUNCTION TESTS IN 10 CASES OF ASBESTOSIS

Case No.	Date	Age (Yrs.)	Sex	SA (m^2)	M.V.V.$_{F}$ (l./min.)	Ventilation Equivalent for Oxygen		VD/VT × 100	Arterial Blood		Dynamic Compliance (l./cm.H_2O)	At Breaths/min.	Non-elastic Work (kg. m./l.) @ l./min.		Dco at Rest (ml./min./mm.Hg) S.T.P.D.	V.C. (l.)	Dyspnoea	Radiological Stage
						l./100ml.	R.Q.		HbO_2%	Pco_2								
1	Jan., '56	62	M	1·65	45	4·1	0·69	67	89·5	36	—	—	—	—	—	—	5	III
	Nov., '58	65			41	6·3	1·00	65	95	31	0·038	39	0·103	32·0	6·80	1·83	5	III
2	Sept., '56	63	M	1·53	60	3·4	0·95	46	93·5	36	0·039	30	—	—	—	—	3	II
	Aug., '58	65			40	2·9	0·66	63	93·5	44	0·028	33	0·070	16·9	4·92	1·55	3·5	II
3	June, '57	59	M	1·62	80	—	—	—	—	—	0·176	31	0·034	16·0	—	—	3	II
	Nov., '58	60			56	3·8	0·75	64	90	36	0·056	40	0·101	22·5	7·32	2·57	3·5	II
4	June, '57	53	M	1·93	31	—	—	—	—	—	0·044	17	0·128	11·8	—	—	3	II
	Aug., '58	54			33	2·6	0·79	60	84	52	0·036	—	0·099	—	4·44	1·30	4	II
5	June, '57	53	M	1·49	67	—	—	—	—	—	0·073	24	0·042	15·7	—	—	3	II
	Dec., '58	54			57	5·8	1·01	58	92	30	0·047	25	0·093	14·8	10·8	1·55	3·5	II
6	Dec., '57	52	M	1·45	43	3·6 (*b*)	1·00	41 (*b*)	93 (*b*)	35 (*b*)	0·066	20	0·086	12·3	8·03 (*b*)	—	3	I
	Dec., '58	53			33	3·5	0·78	62	90	40	0·049	27	0·078	15·4	10·40	1·91	3	I
7	May, '56	51	M	1·75	75	2·7	0·74	40	92·5	37	0·100 (*c*)	—	—	—	—	—	2	II
	June, '58	53			64	3·1	0·79	44	94	32	0·064	29	0·068	28·7	8·65	2·22	3	II
8	June, '58	51	M	1·55	62	3·4	0·81	51	94	35	0·044	34	0·051	33·3	7·65	2·19	3	II
9	June, '57	50	F	1·56	23	—	—	—	—	—	0·073	20	0·039	11·8	—	—	2	II
	Dec., '58	52			33	3·7	0·68	54	92	29	0·062	26	0·037	14·7	5·32	1·61	3	III
10	Feb., '57	46	F	1·40	31	2·8	0·71	57	87	41	0·040	18	0·025	10·0	—	—	3·5	II
	Apr., '57	46			—	2·8	0·83	—	—	—	—	—	—	—	6·24 (*d*)	—	3·5	—
	Feb., '59	48			31	3·3	0·86	42	89	36	0·032	23	0·033	9·0	8·05	1·20	3	II
Mean of most recent observations		56		1·59	45·0	3·39 (*a*)	0·81	56·3	91·4	36·5	0·046	31	0·073	20·8	7·44	1·80	—	—

(*a*) Omitting results with R.Q. over 0·9.
(*b*) During exercise.
(*c*) By method of Mead and Whittenberger, 1953.
(*d*) Using Arterial Pco_2 of Feb., '57.

Dyspnoea: 2 = Can keep up with subjects of own age on the flat but not on gradients.
3 = Cannot keep up on flat but can walk 1 mile or more at own pace.
3·5 = Cannot walk more than 400 yards on flat.
4 = Cannot walk more than 100 yards on flat.
5 = Breathless washing, dressing and talking.

TABLE 6

LUNG FUNCTION TESTS IN 11 LAGGERS WITHOUT RADIOLOGICAL ASBESTOSIS

Case No.	Exposure to Asbestos (Yrs.)	Age (Yrs.)	Sex	SA (m^2)	M.V.V.F. (l./min.)	Ventilation Equivalent for Oxygen		$\frac{VD}{VT} \times 100$	Arterial Blood		Dynamic Compliance (l./cm.H_2O)	At Breaths/ min.	Non-elastic Work (kg.m./l.) @ l./min.		Dco at rest (ml./min mm.Hg) S.T.P.D.	V.C. (l.)	Dyspnoea
						l./100 ml.	R.Q.		HbO_2%	Pco_2							
11	22	64	M	1·90	72	2·5	0·89	49	90	49	0·140	11	0·058	10·5	36·40	3·18	1
12	36	63	M	1·95	84	3·0	0·78	48	91	31	0·118	19	0·073	21·7	10·30	2·02	3
13	45	62	M	1·85	76	2·7	0·76	40	96	34	0·139	24	0·062	23·1	12·90	2·31	1
14	18	52	M	1·85	115	2·9	0·81	44	—	40	0·117	30	0·025	18·9	12·85	3·39	0
15	23	49	M	1·98	116	3·9	1·10	26	—	27	0·115	16	0·044	17·3	14·70	2·69	1
16	4	48	M	1·80	96	2·9	0·69	57	—	39	0·088	26	0·041	14·9	18·35	3·19	0
17	29	46	M	1·64	134	2·4	0·80	40	—	36	0·662	21	0·000(*b*)	—	15·90	3·46	0
18	12	46	M	1·77	106	2·1	0·72	28	—	33	0·116	18	0·024	18·8	6·85	3·76	0
19	30	44	M	1·67	89	3·3	0·98	36	—	33	0·159	28	0·047	15·8	11·88	2·94	0
20	9	39	M	1·90	124	2·4	0·90	34	—	40	0·184	7	0·000(*b*)	—	15·30	4·50	0
21	1	35	M	1·62	104	3·3	0·96	31	—	30	0·246	20	0·011	16·3	12·95	3·74	0
Mean	20·8	50	—	1·81	101·5	2·61(*a*)	0·85	39·4	—	35·6	0·189	20	0·035	17·5	15·31	3·20	—

(*a*) Omitting results with R.Q. over 0·9.
(*b*) Too small to measure.

Dyspnoea: 0 = No dyspnoea.
1 = Probably as good as others of his age.
3 = Cannot keep up on the flat but can walk 1 mile or more at his own pace.

TABLE 7

THE AVERAGE RESULTS OF TESTS IN 10 CASES OF ASBESTOSIS AND IN 11 RADIOLOGICALLY NORMAL ASBESTOS WORKERS, WITH THE PROBABILITY OF THE DIFFERENCES BEING DUE TO CHANCE (t TEST)

	Dust Exposure (Yrs.)	Compliance (l./cm.H_2O)	Vital Capacity (Litres)	Dco (ml./min./mm.Hg)	M.V.V.F. (l./min.)	Non-elastic Work (Kg.m./l.)	Ventilation Equivalent for O_2	$\frac{VD}{VT} \times 100$
Asbestosis	24·7	0·046	1·80	7·4	45·0	0·073	3·39	56·3
Controls	20·8	0·189	3·20	13·2*	101·5	0·035	2·61	39·4
Probability	<0·6	<0·001	<0·001	<0·001	<0·001	<0·001	<0·01	<0·001

*Omitting Case No. 11.

during normal respiration. It is therefore a dynamic rather than a static compliance and the higher frequency of respiration in the patients with asbestosis probably accounts for a part of the difference between them and the controls. A reading approaching the static compliance can be obtained during very slow expiration (Butler, White, and Arnott, 1957) and this was recorded in some of these cases. It was not easy, however, to interpret the results of this test because the compliance was not constant, tending to be lower at the extremes of inspiration and expiration than in the middle range. A mean figure for the middle range was obtained in six cases. In four this was much lower than normal (though always higher than the dynamic compliance) and ranged from 0·042 to 0·069 l./cm.H_2O. In the other two (Cases 3 and 6) "static" compliance was 0·132 and 0·147 l./cm.H_2O respectively. The discrepancy between static and dynamic compliances implies that during normal respiration the lung is not expanding uniformly. The probable reason for this is an irregular distribution of bronchiolar blockage and the figures obtained for non-elastic work support the conclusion that bronchiolar blockage is present in these cases.

The finding of a low pulmonary compliance in asbestosis offers an explanation for the low vital capacity found in these subjects. In order to increase lung volume by two litres from the resting position such a patient must set up a negative intrathoracic pressure of 44 cm. H_2O (on the average) and of up to 72 cm. H_2O in one case. This is beyond the capacity of many healthy adults.

The mean vital capacity in the cases of asbestosis was 1·80 litres. In the asbestos workers without radiological evidence of asbestosis it was 3·20 litres. This difference is statistically significant ($p<0·001$) and is too great to be due to differences in age or size. There is a significant correlation between dynamic compliance and vital capacity whether the latter is expressed in absolute figures or as a fraction of the value predicted from the patient's height using the formula of Needham, Rogan, and McDonald (1954). Correlation coefficients, in the patients with asbestosis, were:

r (absolute) = + 0·528 ($p<0·05$)
r (fraction of predicted) = + 0·426 ($p<0·05$)

Diffusing Capacity.—The mean diffusing capacity for carbon monoxide (Dco) of the 10 patients measured at rest was 7·4 compared with 13·2 ml./min./mm.Hg in 10 of the 11 controls. The difference between these means is significant ($p<0·001$). The figure obtained in the controls was somewhat lower

than the mean normal resting Dco of young adults (Filley, *et al.*, 1954).

The Dco in one of the control subjects was surprisingly high and this figure has been omitted in the calculation of the mean. A second determination in the same subject a year later gave the figure of 12·8 ml./min./mm.Hg so that the first figure was probably incorrect.

Maximum Voluntary Ventilation and Work of Breathing.—In the patients with asbestosis the mean M.V.V. was 45·0 l./min. The mean for the controls was 101·5 l./min. and, though their average age is less, the difference between the two is certainly significant ($p<0.001$). The loss of ventilatory ability is related to loss of vital capacity, ($r = +0.790$ $p<0.02$). The correlation between M.V.V. and compliance at +0·521 is also significant ($p<0.05$). It should, in theory, be possible for the patient with a restricted vital capacity to counteract the effect of this on the M.V.V. by increasing the frequency of respiration, but this will only be possible if there are no factors limiting speed of movement. In fact there is, in these patients, an increased resistance in the lungs and airways, the best measure of which is the non-elastic work of respiration (Leathart, 1959). The mean in the patients was 0·073 kg. m./l., and in the controls 0·035. This difference is significant at the 0·1% level. The upper limit of normal is 0·035 kg. m./l. It is therefore clear that there is an increased resistance to movement in the asbestotic lung. This resistance plays a part in reducing the M.V.V. (correlation coefficient $= -0.817$, $p<0.001$) and it also affects the distribution of air during inspiration and thus lowers the dynamic compliance below the "static" compliance. This difference was very obvious in Case 3 who also had very high lung resistance. Marshall and Dubois (1956) found that both the airway resistance and the lung viscosity were high in their patient. It is not possible to deduce from the present results whether the resistance is mainly in the lung tissue or in the airways, but the fact that bronchographic evidence of bronchitis, if not of bronchiectasis, was found in most patients suggests that part, at least, of the resistance lies in the airways.

Ventilation Equivalent and Arterial Pco_2.—The number of litres of air breathed for every 100 ml. of oxygen absorbed (Knipping and Moncrieff, 1932) is a measure which must be interpreted with caution, because it is influenced by emotional hyperpnoea. When this is present the respiratory quotient is increased. In this paper only those ventilation equivalents which were obtained at a R.Q. of less than 0·9 are considered. Subject to this condition the mean for the patients with asbestosis was 3·39, and for the controls was 2·61. This difference is significant at the 1·0% level. The normal figure is about 2·5 so that the ventilation equivalent of the controls is within normal limits but in asbestosis it is abnormally high, and indicates the presence of hyperventilation at rest. The mean arterial Pco_2 was not significantly different in the two groups of subjects. However, the tension was below the mean normal level in 11 of the 16 blood samples derived from the asbestosis cases. This is a striking contrast to the arterial Pco_2 in emphysema which is usually above normal and sometimes grossly raised. It implies that the excessive ventilation is not initiated reflexly by CO_2 retention but may be due, either to the arterial desaturation, or to reflexes arising in the stiff lungs.

Dead Space Effect.—The normal dead-space effect (D.S.E.), calculated from the formula given by Donald (1953), is 30-40% of the tidal air. The mean D.S.E. in the controls was 39·4% but in the cases of asbestosis it was 56·3%, which is abnormal. The difference between the means is significant at the 0·1% level. Such an increase in D.S.E. is partly due to ventilation occurring at a rapid rate with small tidal excursions, and in part represents ventilation of underperfused alveoli: but in the present series it was not associated with the presence of bronchiectasis. It indicates that there are inequalities of ventilation/perfusion ratios in the lungs of most cases of asbestosis. This conclusion is supported by the observation that the diffusing capacity was not low enough to account for the observed degree of arterial desaturation in Cases 3, 5, 6, 9, and 10, in whom venous admixture must have been present. In Case 4, however, the mean pulmonary capillary oxygen tension (calculated from the observed oxygen uptake, Dco $\times$ 1·23, and ideal alveolar Po_2) was only 27 mm. Hg. A similar instance of apparent discrepancy between diffusing capacity for carbon monoxide and for oxygen was recorded by Bates (1958) in the Hamman-Rich syndrome.

Since this paper was written a further case has been examined and has shown similar results. The compliance was 0·018 (dynamic) 0·020 (static) l./cm.H_2O and the Dco was 8·7 ml./min./mm.Hg. Vital capacity was 0·82 l. and $M.V.V._F$ was 59 l./min.

Discussion

As the patients with asbestosis had all been referred to hospital the results obtained in this series of patients probably represent the effects of fairly advanced disease, and this may account for the discrepancies between this and previous work,

notably that of Bader *et al.* (1957). Bronchiectasis, which is a late manifestation of the disease (Stone, 1940) was present in six cases. Bronchiectasis must contribute to the functional abnormalities in these patients, but its effect is considered to be small because those cases in whom bronchiectasis could not be demonstrated showed abnormalities of the same type and degree as those in whom it was obvious. Moreover, the functional changes which occur in bronchiectasis, even when it is severe and bilateral, are, in my experience, seldom so marked as those seen in asbestosis. In particular the diffusing capacity is not greatly reduced and the pulmonary compliance is usually normal. Kamener, Becklake, Goldman, and McGregor (1958) recorded a compliance of more than 0·091 l./cm. H_2O in three of the four cases of bronchiectasis whom they examined preoperatively but they suggest that the rather low postoperative findings (range 0·059 to 0·352; mean 0·125) indicate that compliance is decreased in this disease. At all events the decrease is mild. It is therefore suggested that the function changes reported in this paper were mainly the direct effect of asbestosis, and that the secondary bronchiectasis contributed little to them.

Pulmonary Compliance and Diffusing Capacity.—The results in this series of 10 cases confirm the finding of Marshall and Dubois (1956) that the lungs are abnormally stiff in asbestosis. The very low compliance found in asbestosis, often without much radiological abnormality, is in striking contrast to the slight decrease found in progressive massive fibrosis of coal-miners (Leathart, 1959). This difference may arise because the fibrosis is generalized, or pleural, in asbestosis, while in P.M.F. it is localized.

The well-marked reduction of diffusing capacity in asbestosis confirms the finding of Marks *et al.* (1957), and of Bader *et al.* (1957) and justifies the deductions of Baldwin *et al.* (1949), Wright (1955) and Sartorelli (1957), especially as it was recorded in the presence of excessive ventilation, which is known to increase the Dco (Ross, Frayser, and Hickam, 1958). It will be noted that although the changes in compliance and in Dco are both presumably due to pulmonary fibrosis there is no demonstrable correlation between the two. All 10 cases had a low compliance but the diffusing capacity was just within normal limits (above 10 ml./min./mm.Hg) in two of them. Presumably the fibrosis in the lungs of these two patients (Cases 5 and 6) must have been so placed (septal, peribronchial, or pleural) that it caused no significant loss of alveolar surface area. There was radiological evidence of pleural thickening in one of these patients but not in the other. There were no cases in whom the diffusing capacity was low while pulmonary compliance was normal so that hypertrophic emphysema, which is a common cause of loss of alveolar surface area, does not play an important part in reducing diffusing capacity in this disease. Gaffuri and Berra (1957) also concluded (from a study of lung volumes) that emphysema was not a feature of asbestosis. Gloyne (1933) however stated that bullae were occasionally seen at autopsy while Haddow (1929) and Wegelius (1947) reported radiological translucency of the upper lung fields.

It has been calculated that the steady-state Dco is affected by inequalities of ventilation/volume ratio in the lung. This reduces the apparent Dco (Forster, Fowler, and Bates, 1954). This effect may have exaggerated the abnormality in Case 4 but it is believed to have been of minor importance in the other nine cases in whom the apparent Dco was not low enough to account for the degree of arterial desaturation recorded at rest.

Maximum Voluntary Ventilation and Vital Capacity.—The demonstration of a low mean M.V.V. in the present series confirms the work of Roemheld *et al.* (1940), Bastenier *et al.* (1955) and Gaffuri and Berra (1957) but is contrary to the experience of Baldwin *et al.* (1949) of Wright (1955) and of Bader *et al.* (1957). All workers except Bader and his colleagues agree that a low vital capacity is usual, and in the present series the values have fallen between the very low ones of Roemheld *et al.* (1940) and the relatively high ones of Gaffuri and Berra (1957). A significant correlation between maximum ventilation and vital capacity was demonstrated in the present investigation, and in the results of Gaffuri and Berra (1957). The non-elastic work of breathing was found to be high in these 10 cases and to correlate well with reduction of M.V.V. This suggests that an increase in pulmonary resistance plays a part in reducing the M.V.V. The one second forced expiratory volume was a rather low fraction of the vital capacity in Gaffuri and Berra's cases and in those of Bastenier *et al.* (1955). In the presence of a low vital capacity this probably has more significance than the authors attribute to it and also suggests the presence of an increased resistance to air-flow.

Hyperventilation.—Roemheld *et al.* (1940), Gernez-Rieux *et al.* (1954), Bastenier *et al.* (1955), Wright (1955) and Bader *et al.* (1957) all refer to hyperventilation in asbestosis, but respiratory quotients have not been published and it is uncertain whether their patients were in a steady state. The ventilation equivalents reported in this paper confirm that hyperventilation at rest is a feature of asbestosis but

not specific, as it is common in many respiratory and cardiac ailments (Knipping and Moncrieff, 1932).

Relation Between Functional and Radiological Changes.—Roemheld *et al.* (1940) and Gaffuri and Berra (1957) demonstrated a clear correlation between loss of vital capacity and the severity of radiological abnormality and in the second paper this applied to the indirect M.B.C. also. Bastenier *et al.* (1955), Wright (1955) and Amsler (1958) have concluded that there is no such relationship. Although the number of cases examined in the present investigation is small it can be said that there is no evidence to support Gaffuri and Berra. Moreover, many of the cases were examined on more than one occasion and functional deterioration was demonstrated in most while radiological progression occurred only in Cases 2 and 9. It therefore seems unlikely that there is a close correlation between functional and radiological abnormalities. The one case with Stage 1 radiological changes showed functional evidence of progressive fibrosis, which suggests that radiological changes may not develop until late in the disease.

The Use of Pulmonary Function Tests as an Aid to the Diagnosis of Asbestosis.—Highly significant differences between patients with asbestosis and asbestos workers with normal radiographs have been established in seven different tests (Table 7). Some of these tests, however, are far from being specific for this disease and, in so far as asbestosis is defined as "fibrosis of the lungs due to asbestos dust", only the measurement of pulmonary compliance and of diffusing capacity (plus those other tests which largely depend on these two factors) would be expected to be of diagnostic value.

Low pulmonary compliance is an outstanding feature of this disease, but dynamic compliance of a similar order is occasionally found in other pulmonary fibroses (Marshall and Dubois, 1956) and also in heart failure (Saxton, Rabinowitz, Dexter, Haynes, and Walker, 1956; Sharp, Griffith, Bunnell, and Greene, 1958). Thus this observation cannot be regarded as diagnostic but it has confirmatory value in the presence of a history of exposure to asbestos dust.

The finding of a low diffusing capacity is of less value in confirming the diagnosis of asbestosis because there are many other conditions in which it is reduced. It is of more significance when combined with the finding of a low compliance.

The presence of these two abnormalities of function does no more than confirm the diagnosis. The absence of both almost certainly rules out the possibility of asbestosis, and this has been found useful for excluding the diagnosis in patients who have been exposed to silica, coal, and iron dusts as well as to asbestos and in others whose chest radiographs are equivocal.

It will be noticed, however, that the pulmonary compliance was normal (0·176 l./cm. H_2O) when first measured in Case 3. The static compliance was again normal when the measurement was repeated 17 months later and this single aberrant case suggests that the change in pulmonary compliance may be a comparatively late feature of the disease.

The functional anomalies reported here have all occurred in the presence of radiologically obvious disease. Presumably lesser abnormalities are present at an earlier stage, so that the observation of progressive alteration of function might be used to make an earlier diagnosis. Particular attention should be paid to the measurement of vital capacity. The other tests described here cannot be applied in the factory, but it is probable that the single breath measurement of Dco (Ogilvie, Forster, Blakemore, and Morton, 1957) and the step test for hyperventilation (Hugh-Jones, 1952) would also reveal progressive deterioration.

Lung Disease Without Radiological Abnormality.—Wright (1955) and Amsler (1958) have both stressed that functional changes and disability may occur in asbestos workers with normal radiographs. It is doubtful, however, whether this should be regarded as an expression of early asbestosis or even as being due to asbestos dust, since functional changes and disability without radiological abnormality are common in all walks of life.

In the present investigation respiratory symptoms, and dyspnoea in particular, have been uncommon in the asbestos workers without radiological abnormality (the controls). Mild degrees of functional

TABLE 8

RESULTS IN ASBESTOS WORKERS WITHOUT RADIOLOGICAL ABNORMALITY AS A PERCENTAGE OF PREDICTED VALUES

Case No.	M.V.V.[1] (%)	Compliance[2] (%)
11	72	78
12	82	63
13	76	80
14	104	68
15	98	59
16	85	54
17	124	474
18	92	73
19	79	110
20	98	102
21	87	183
Mean	91	123

[1] M.V.V. predicted = B.S.A. × 40 − (1·1 × Age) + 94 (Needham *et al.* 1954).

[2] Compliance predicted = B.S.A. × 0·1594 − 0·122 (Marshall, 1957).

abnormality have been recorded and are set out in Table 8 as percentages of predicted values.

As the formula of Needham *et al.* (1954) for prediction of M.V.V. is based on the best of two or three attempts while the M.V.V. given in this paper is the average of three it is likely that only ratios of less than 80% indicate real abnormality. There were only three such ratios and the mean of the series was normal.

Seven of the control subjects had pulmonary compliances of less than the predicted value; nine of them gave a figure lower than the average obtained in eight colliery employees, of similar age, who had never worked underground (Leathart, 1959) and lower than normal (Frank, Mead, Siebens, and Storey, 1956). Case 16 gave a figure below the lower limit of normal and when this was repeated a few days later a figure of 0·094 l./cm.H_2O was obtained. These considerations all suggest that there may be some alteration in the lungs of asbestos workers before abnormalities appear on the radiographs. There are, however, a number of arguments to set against this. First, the difference between the laggers and colliery surface workers may have been due to chance ($p>0·3$); secondly, experience with Case 3 is opposed to the findings in Case 16; thirdly, the "static" compliance in Case 16 was normal, being 0·143 l./cm. H_2O on the first occasion and 0·263 l./cm. H_2O a few days later. This observation, and the finding of a dead space effect of 57%, suggest that distributional defects may have caused a falsely low dynamic compliance in this case. Moreover, this one man, whose compliance was most abnormal, had had only four years exposure to asbestos dust, compared with over 20 years in six of the other controls.

Thus, this study has not produced convincing evidence that fibrosis of the lung occurs in asbestos workers before changes appear on the radiograph. A larger number of asbestos workers must be investigated before any firm conclusion can be reached.

It is possible, however, that infiltration of the lung may precede fibrosis and that this may, as in the early stages of sarcoidosis, affect the diffusing capacity without causing much alteration of pulmonary compliance (Marshall, Smellie, Baylis, Hoyle, and Bates, 1958). In the present investigation the diffusing capacity of the control subjects tended to be at the lower end of the normal range, but it is clear from the work of Donevan, Palmer, Varvis, and Bates (1959) that this reduction may be due to the age of the subjects, rather than to pulmonary infiltration, for the diffusing capacity was normal in two of the patients who had definite asbestosis. In control Case 18, however, the Dco was undoubtedly abnormal. The measurement was repeated four months later and found to be slightly lower, so that this finding was probably not due to an analytical error. The pulmonary compliance was less than normal in this subject but there was no other abnormality and he had no respiratory symptoms. This appears to be the only case in whom there is a definite possibility of undiagnosed asbestosis and he is being carefully watched. In the other cases with a rather low diffusing capacity it cannot be said whether this is due to the earliest stage of asbestosis or due to other disease (chronic bronchitis and emphysema) resulting from prolonged inhalation of an irritant dust.

Progression of the Disease.—In nine cases, measurements of M.V.V. and of compliance had been made 12 to 34 months before the results discussed so far. The M.V.V. was usually larger on the first occasion, but was virtually the same in three cases and slightly smaller in one. The compliance was higher in six cases and about the same in three others. If the alteration in these figures is divided by the time interval between recordings, to get a figure representing rate of progression, the figure varies greatly from case to case, and this agrees with clinical experience. However, the general tendency is for worsening to occur and improvement is exceptional. It should be pointed out that when Case 10 was first investigated she was in hospital recovering from broncho-pulmonary infection. Hence slight improvement in some tests is not surprising.

The Cause of Dyspnoea in Asbestosis.—In asbestosis dyspnoea occurs on exertion but the tests described in this paper, and most of the tests done by other workers, have been carried out at rest. Hence any deduction from these tests concerning the cause of dyspnoea involves the assumption that respiratory function does not improve with exercise. The literature on asbestosis does not contain any specific investigation of this point but Bastenier *et al.* (1955) demonstrated that the coefficient of utilization of oxygen decreased in five cases of asbestosis during mild exertion; in normal individuals it remains constant (Knipping and Moncrieff, 1932) or increases (Denolin, 1958). Whereas the diffusing capacity normally increases on exertion (Filley *et al.*, 1954); Bates, Knott, and Christie (1956) demonstrated that when the Dco has been lowered by disease this increase is small or absent. Consequently one might expect little alteration in the diffusing capacity in asbestosis during exertion and in the one case in whom it was measured it was found to be slightly lower than the resting value. It therefore is probably

justifiable to assume that in asbestosis the diffusing capacity and the ventilation equivalent for oxygen do not alter with exertion. In addition to this, numerous investigations have established that the ventilation during exertion does not exceed the M.V.V. at rest (Simonson and Enzer, 1942; Dripps and Comroe, 1947; Slonim, Gillespie, and Harold, 1957).

Baldwin *et al.* (1949) and Wright (1955) regard hyperventilation during exercise as an important factor in the dyspnoea of asbestosis while Roemheld *et al.* (1940), Sartorelli (1957) and Amsler (1958) stress the defective uptake of oxygen in this disease. Among the 10 cases investigated here, however, it can be shown that, while the diffusion defect limits oxygen uptake in half the cases, the restriction of ventilatory ability plays an equal or more important part in the other half. The calculations on which this conclusion is based are given in Appendix 2.

Conclusions

It has been shown that a low vital capacity accompanies fibrosis of the lungs in asbestos workers. This suggests that the vital capacity of all exposed workers should be measured at regular intervals and that a progressive decline should be taken as a warning of impending disease. The possibility that asbestos dust may damage the lungs without causing fibrosis is best investigated by measuring the diffusing capacity, but the results of such an investigation must be interpreted with caution.

I am grateful to Professor R. C. Browne for permission to examine his patients and for clinical details of many of them, to Mr. D. J. Newell and Mrs. D. Weightman for statistical advice and calculations, to the staff of the Department of Radiology in the Royal Victoria Infirmary for their cooperation, and to Miss P. Peyton for clerical work.

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APPENDIX 1

Occupational Histories

Case No.	Chief Occupation		Other Work	
	Age (Years)	Description	Age (Years)	Description
Patients with Asbestosis:				
1	26-59	Pipe and boiler coverer. This work entailed stripping the old asbestos lagging from the pipes and boilers of ships, mixing and dampening dry insulating material (asbestos, magnesia, cement), and the application of this and of dry asbestos slabs.	14-26	Trapper and pony driver in a colliery. He never worked on the coal-face
			59-61	Light labouring
			61-65	Retired
2	14-50 (with breaks)	Work in an asbestos factory where raw fibre was cleaned, teased out, and fabricated into pipe sections, board, mattresses, etc. He worked in almost every department. No carding, spinning, or weaving is done in this factory	21-26	Gymnastic instructor in the Army
			46-48	Gymnastic instructor in the Army
			50-65	Patrol-man and time-keeper in asbestos factory
3	27-54	Pipe and boiler coverer in ships, factories, power stations and underground tunnels. Hazard the same as in Case 1	14-18	Apprentice engineer
			18-22	Barman
			22-23	Unemployed
			23-27	Royal Navy (Minesweeper deckhand)
			54-60	Clerical work
4	14-50	Pipe and boiler coverer in ships and power stations. Last three years work mainly as an overseer. Hazard the same as in Case 1	50-55	Clerical work
5	18-54	Pipe and boiler coverer mainly in ships. Hazard the same as in Case 1	14-17	Cleaning moulds in a glass factory
			17-18	Driving a horse drawn van
6	35-52	Pipe and boiler coverer mainly in ships. Hazard the same as in Case 1	14-20	Bottle-making
			20-35	Roofing and tiling
			52-54	Light labouring away from asbestos dust
7	22-49	Pipe and boiler coverer in ships, factories, and power stations. Hazard the same as in Case 1	14-15	Paint works
			15-20	Core maker in a foundry
			20-22	Unemployed
			49-53	Light work. No contact with asbestos
8	39-40	Moulding wet asbestos in the fabrication of pipe-sections	16-38	Machinist
	41-48	Filling bags with a dry mixture of asbestos and magnesia	38-39	Unemployed
	48-50	Filling bags with a dry mixture of asbestos and calcium silicate	50-51	Time-keeper in asbestos factory
9	20-23	Filling hoppers with raw asbestos	15-20	Hospital ward maid
	23-31	Rolling out pipe-sections in damp asbestos fibre	31-35	Cinema usherette
			35-52	Housewife
10	17-26	General labouring in an asbestos factory carrying, measuring, and stacking asbestos pipe sections	26-32	Housewife
			43-44	Unemployed
	34-41	Rubbing down asbestos pipe-section insulators to the correct size	44-46	Clerk
	41-43	Steel band machine attendant in asbestos factory, in the same workshop as previous work		
Control Subjects:				
11	42-64	Lagger in a power station. Same hazard as Case 1	14-15	Milk roundsman
			15-19	Colliery surface worker
			19-24	Royal Navy (stoker)
			24-29	Builder's labourer
			29-31	Ash plant attendant
			31-41	Coal belt attendant
			41-42	Fitter's mate
12	27-63	Lagging at a power station	14-20	Brass turning
			20-24	Army
			24-27	Brass turning
13	14-18	Lagger's mate } in ships and factories	18-21	Army
	21-38	Lagger }		
	38-62	Lagger in a power station		
14	30-35	Lagging at a power station	14-16	Apprentice joiner
	39-52	Lagging at a power station	16-21	Candle maker
			21-30	Engine-room cleaning at power station
			35-39	Flight mechanic R.A.F.
15	18-26 }		13½-16	Catcher lad in a shipyard
	28-30 }	Lagger's mate and lagger in ships factories and power station	16-18	Steel plate marker
	36-44 }		26-27	Out of work
	44-49	Lagger in a power station	30-36	Army (some lagging done in the Army)
16	44-48	Lagger's mate in a power station	14-20	Labourer in a foundry. Never shook out or cleaned castings
			20-33	R.A.F. (Armourer)
			33-35	Railway porter
			35-40	Plumber's mate (domestic plumbing)
			40-44	Expander in constructional engineering works
17	17-38	Lagger in ships	14-17	A duffer in a wool mill
	38-46	Lagger in a power station		
18	34-46	Lagger in a power station	14-18	Delivering milk
			18-20	Bricklayer's labourer
			20-25	Fitter's mate
			25-30	Concreting
			30-34	Army
19	14-44	Lagging in power stations		
20	30-39	Lagger's mate in a power station	14-16	Errand boy
			16-21	Apprentice boiler-maker in shipyard
			21-24	Boiler-maker
			24-28	Army
			28-30	Caulker
21	34-35	Lagger's mate in a power station	14-17	Delivery boy
			17-18	Machinist in engineering works
			18-22	Royal Navy (stoker)
			22-31	Dining car attendant
			31-34	Power station auxiliary plant attendant

APPENDIX 2

Calculation of Factor which Limits Oxygen Uptake

If the diffusing capacity for oxygen is known (it is equal to Dco × 1·23), the ideal alveolar oxygen tension is known, and the mean pulmonary capillary oxygen tension is assumed to fall to zero during exercise, then the maximum rate of oxygen uptake can be calculated. When the ventilation equivalent for oxygen is known the ventilation required for this uptake can be calculated. If this figure exceeds the M.V.V. it is clear that exercise will be limited by the M.V.V. but if it falls short of the M.V.V. the limit will be set by ability to absorb oxygen. These calculations have been made in the 10 cases of asbestosis and are given in the Table. In this table Do_2 is given at ambient temperature and pressure saturated, and ideal alveolar oxygen tension is calculated from the formula: Ideal alv. Po_2 = Inspired Po_2 minus

$$\text{Arterial } Pco_2 \times \left(0{\cdot}21 + \frac{0{\cdot}79}{\text{R.Q.}}\right)$$

It can be seen that in five cases the maximum rate of oxygen uptake is limited by the diffusing capacity while in the other five the reduction of M.V.V. plays an equal or more important part. This conclusion is not altered if a more reasonable figure for mean capillary oxygen tension (*e.g.*, 30 mm.Hg) is assumed, or if the ventilation equivalent in Cases 1 and 5, who were demonstrably hyperventilating when the quoted figure was obtained, is taken to be equal to the mean of the other eight cases, *i.e.* 3·4. But if these alterations are made simultaneously it is found that M.V.V. limits oxygen uptake in only three cases.

TABLE

MAXIMUM OXYGEN UPTAKE AND M.V.V. IN ASBESTOSIS

Patient	Calculated Alveolar Po_2	Do_2	Maxm. O_2 Uptake (ml./min./mm.Hg)	Ventilation Equivalent	Ventilation Required (l./min.)	M.V.V. (l./min.)	Limit
1	117	9·05	1060	6·25	66·2	41	M.V.V.
2	84	6·45	542	2·9	15·7	40	Do_2
3	105	9·72	1050	3·8	39·9	56	Do_2
4	84	5·58	468	2·6	12·4	33	Do_2
5	120	14·32	1740	5·8	99·5	57	M.V.V.
6	96	15·10	1450	3·5	50·6	33	M.V.V.
7	108	11·58	1250	3·1	38·8	64	Do_2
8	107	10·43	1120	3·4	38·0	62	Do_2
9	111	7·08	787	3·7	29·1	33	Both
10	111	10·40	1150	3·3	38·0	31	M.V.V.

Brit. J. industr. Med., 1960, **17**, 228.

THE MEASUREMENT OF OCCUPATIONAL MORTALITY

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(RECEIVED FOR PUBLICATION MAY 6, 1959)

In making comparisons of the mortality of different occupational groups, it is essential to allow for differences in the age distributions of the groups. The principle of "standardizing" for age is long established. Each of the two conventional methods, direct and indirect, leads to a "Standardized Mortality Ratio" (S.M.R.) which is a weighted average of the ratios of the death rates, by ages, in the occupation, to the corresponding death rates in some standardizing population. In both methods, very great weight is given to the ratio obtained from the oldest age groups. Previous research has shown that there is serious distortion in the recording of occupations, which is greatest among the oldest age groups; the S.M.R.s based on the conventional methods are thus liable to serious error, as well as to "bias".

A more recent method, inverse, of particular use when the age distribution of the occupation is unknown, gives more equal weights to the ratios of the death rates for the various age groups. The S.M.R. calculated by it, therefore, generally differs markedly from those obtained by the conventional methods.

In a fourth, apparently new method, the weighting of the ratios of death rates is again more uniform than in the conventional methods; it has the further advantage of being based on the age distribution of the standardizing population rather than that of the occupation itself as is the case with the third, inverse, method. This "new" method of obtaining an S.M.R., for comparing the mortality of the occupational group as a whole, is therefore the one which is least open to objection on logical grounds.

However, each of the four methods, and of two others given in the literature, is an attempt to compare one occupation with some standard in terms of a single index, averaging the ratios of the death rates by ages. Such an index can take no account of the variation between these ratios and since this variation is often very great none of the methods can fail to be misleading in many cases. Further, the standard deviation of each index takes no account of this variation and so can be misleading also.

The realization that hazards to health vary between occupations dates back at least to Hippocrates, but the measurement of occupational mortality seems to have started with the Census of 1851 in Great Britain (Registrar-General, 1855). The convention of measurement is straightforward. Denominators of mortality rates are obtained from Census Schedules, on which, from 1851 onwards, every member of the population has to be recorded together with his age and occupation. Numerators come from Registrations of Death, which also contain information about age and occupation. The definitions of occupation are nominally exactly the same in these two sources (General Register Office, 1951). Usually, comparisons of occupational mortality are restricted to the ages 20 to 64, and, for men, relate to all males, including both occupied and retired men. (See Benjamin, 1959, for a fuller discussion.)

This paper discusses the measurement of occupational mortality, in terms of the two conventional and some newer methods. The argument is illustrated by the material in Table 1, which is taken from the Registrar-General's Decennial Supplement (1958b).

Because of the wide variation in death rates with ages, the differences in the age distribution of the populations have to be allowed for. The principle of "standardizing" for age has long been established and there are two conventional methods, direct and

TABLE 1

POPULATIONS AND DEATHS OF ALL MALES AND COALMINERS IN 1951

Age Group	All Males			Hewers and Getters in Coal-mines			Other Coalminers		
	Census Population (thousands)	Deaths*	Death rate per thousand	Census Population (thousands)	Deaths*	Death rate per thousand	Census Population (thousands)	Deaths*	Death rate per thousand
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
20 to 24	1,427·2	1,973·4	1·38	13·6	24·4	1·79	26·3	43·8	1·67
25 to 34	3,139·7	5,003·6	1·59	52·3	97·8	1·87	71·8	129·0	1·80
35 to 44	3,290·4	9,437·2	2·87	50·6	184·0	3·64	83·8	268·8	3·21
45 to 54	2,874·3	23,604·0	8·21	39·0	430·6	11·05	87·4	689·6	7·89
55 to 64	2,028·1	46,550·4	22·95	21·1	870·0	41·20	62·9	1,307·8	20·80
20 to 64	12,759·8	86,568·6	6·78	176·6	1,606·8	9·10	332·1	2,439·0	7·34

*One-fifth of the deaths registered over the five years 1949-53.

indirect. The term "Standardized Mortality Ratio" strictly refers only to the measure produced by the indirect method, but for convenience in this paper the various measures discussed are all called S.M.R.s and are differentiated by indicating the method used.

Methods of Obtaining Standardized Mortality Ratios

In the direct method, the death rates for one particular occupation are applied to the population of all males, to obtain the number of deaths which would have occurred in the all males population, and this number is compared with the number of deaths actually observed for all males. Thus, from Table 1, for Hewers and Getters, the figures of column (2) are multiplied by those of column (7) to give

$1{,}427{\cdot}2 \times 1{\cdot}79 + \ldots + \ldots + \ldots + \ldots = 135{,}722$

deaths which would have occurred compared with 86,568·6 recorded. The ratio of these figures, expressed as a percentage (*i.e.*, $100 \times 135{,}722 \div 86{,}569 =$) 157, is called here the S.M.R. (direct). The usual name for this ratio is Comparative Mortality Figure (Registrar-General, 1938).

In the indirect method, the death rates for all males are applied to the population of the particular occupation, to obtain expected deaths, which are related to the deaths observed. Thus from Table 1, for Hewers and Getters, the figures of column (5) are multiplied by those of column (4) to give

$13{\cdot}6 \times 1{\cdot}38 + \ldots + \ldots + \ldots + \ldots = 1{,}052$

deaths to be compared with 1,606·8 recorded. The ratio of these figures, expressed as a percentage (*i.e.*, $100 \times 1{,}606{\cdot}8 \div 1{,}052 =$) 153, is the S.M.R. (indirect).

Recently, Kerridge (1958) has introduced to this country* a measure which he calls the inverse S.M.R. This method is to divide the death rates for all males into the numbers of deaths observed in the particular occupation to get an estimate of the population in the occupation which should have existed to "justify" the number of deaths observed. Thus, from Table 1, for Hewers and Getters, the figures of column (6) are divided by those of column (4) to give

$24{\cdot}4 \div 1{\cdot}38 + \ldots + \ldots + \ldots + \ldots = 233.7$

thousand which would have been the size of the population to justify these deaths, whereas there were only 176·6 thousand actually in the population. The ratio of these two figures expressed as a percentage (*i.e.*, $100 \times 233{\cdot}7 \div 176{\cdot}6 =$) 132, is the S.M.R. (inverse).

Kerridge pointed out that the standard error of the inverse S.M.R. is generally greater than that of the conventional ratios (see Appendix for demonstration), and so it might be thought that the differences between the inverse S.M.R. and the others were explained in this way. In Table 2, the S.M.R.s both for Hewers and Getters and for Other Coalminers are given, together with their standard errors calculated on the usual assumption that the variance of the number of deaths in any one age group of the particular occupation is equal to the number of deaths.

TABLE 2

STANDARDIZED MORTALITY RATIOS FOR HEWERS AND GETTERS AND FOR OTHER COALMINERS IN 1951

Method of Standardization	Hewers and Getters		Other Coalminers	
	S.M.R.	Standard Error	S.M.R.	Standard Error
Direct	157	4·0	96	2·0
Indirect	153	3·8	96	1·9
Inverse	132	5·1	105	3·3

Here it can be seen that the standard errors of the inverse S.M.R.s are indeed the highest but that they are not sufficiently high to account for the difference of over 20 points in the S.M.R.s for Hewers and

*Kerridge (1959) has pointed out that, although his method was developed independently, it had been published previously in America (Doering and Forbes, 1939).

Getters. Further the inverse S.M.R. for Other Coalminers indicates mortality experience worse than average whereas the conventional measures indicate experience better than average. It is thus desirable to examine the various methods to see why they differ and to determine a basis for deciding which is the most appropriate of them for any particular purpose.

Let the death rate in one age group in a particular occupation, expressed as a percentage of the death rate in the same age group in the population of all males, be called θ. For Hewers and Getters, the values of the θs are obtained from Table 1 by dividing the figures of column (7) by those of column (4), and multiplying by 100, to give ($100 \times 1{\cdot}79 \div 1{\cdot}38 =$) 130, etc.; for Other Coalminers from column (10) and column (4) to give ($100 \times 1{\cdot}67 \div 1{\cdot}38 =$) 121, etc. These values are given in columns (6) and (9) of Table 3 below.

In the Appendix it is shown that each of the three methods is equivalent to obtaining a weighted average of the θs. Table 3 also gives the weights for the S.M.R.s of Hewers and Getters and of Other Coalminers (obtained from the material of Table 1).

The weightings of the θs for the direct method are by the deaths amongst all males, in the age groups, which are given in column (3) of Table 3. It can be seen that over half the weight (53·8%) is given to the θ for the oldest group, and another quarter of the weight (27·3%) to the θ for the next oldest group. These S.M.R.s therefore reflect the mortality experience of the oldest men and take practically no account of that of younger men. Since the θs for the two oldest groups of Hewers and Getters, for example, are considerably higher than those for the younger groups, this leads to bias. Similarly, with Other Coalminers, there is a bias in the opposite direction.

For the indirect method, the weightings of the θs are by the expected deaths in the occupations which are given in columns (5) and (8). It so happens that these distributions are similar to those of column (3) and therefore the same effects are observed and the S.M.R.s calculated by the two conventional methods are closely similar; in other occupations the distributions of expected deaths by age may be rather different, but normally by far the greatest weights will be given to the θs for the oldest groups.

For the inverse method, the weightings are by the age distributions of the populations in the occupations, which are given in columns (4) and (7) respectively. These distributions differ appreciably, but are both much more evenly spread over the age groups than are the deaths. Thus for each occupation the θs get comparatively equal weight and the S.M.R. lies more or less in the middle of the range of θs.

A fourth method, which does not appear to have been discussed before, suggests itself. In this the θs are weighted by the age distribution of all males as given in column (2). It is calculated by multiplying the population of all males in each age group by the ratios of the death rates and dividing by the total population of all males. Thus, from Table 1, for Hewers and Getters, the figures of column (2) are multiplied by those of column (7) and divided by those of column (3) to give

$$1{,}427{\cdot}2 \times 1{\cdot}79 \div 1{\cdot}38 + \ldots + \ldots + \ldots + \ldots = 17{,}226$$

The ratio of this figure to that for the all males population, expressed as a percentage (*i.e.*, $100 \times 17{,}226 \div 12{,}760 =$) 135, is the S.M.R. ("new" method). Since the weightings of the θs are by the age distribution of a population, they are broadly similar to those used in the inverse method and the S.M.R.s can be expected to lie in the middle of the spread of the individual θs. They turn out to be 135 for Hewers and Getters and 106 for Other Coalminers, which compare with S.M.R.s (inverse) of 132 and 105 respectively.

Two other broadly comparable methods exist. That of Yule (1934), using the "equivalent average death rate", is, in effect, a weighting of the θs by the population death rates in the age groups; that

TABLE 3

DEATH RATES AS PERCENTAGES OF RATES FOR ALL MALES (θs) AND THEIR WEIGHTS IN S.M.R.s
(Distributions by age of populations, deaths, etc.)

Age Group	All Males		Hewers and Getters			Other Coalminers		
	Population (%)	Deaths (%)	Population (%)	Expected Deaths (%)	Death Rates as % of Rates For All Males (θ)	Population (%)	Expected Deaths (%)	Death Rates as % of Rates For All Males (θ)
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
20 to 24	11·2	2·3	7·7	1·8	130	7·9	1·4	121
25 to 34	24·6	5·8	29·6	7·9	118	21·6	4·5	113
35 to 44	25·8	10·9	28·6	13·8	127	25·2	9·4	112
45 to 54	22·5	27·3	22·1	30·4	135	26·3	28·1	96
55 to 64	15·9	53·8	12·0	46·0	180	18·9	56·6	91
20 to 64	100	100	100	100	134	100	100	108

TABLE 4
RATIO OF DEATH RATES IN OCCUPATIONS TO DEATH RATES FOR ALL MALES

Registrar-General's Large Occupational Groups		Population Aged 20-64 (thousands)	Values of θ					Range of θ	S.M.R. (Indirect)
No.	Brief Description		20-24	25-34	35-44	45-54	55-64		
1	Farmers, etc.	230·1	154	94	79	67	69	87	70
2	Gardeners, etc.	145·4	107	111	88	80	76	35	79
3	Other agricultural workers	334·9	104	96	84	70	72	34	76
4	Coal face getters, etc.*	197·9	128	117	124	130	174	57	148
5	Other Coalminers, underground†	213·8	111	108	112	94	87	25	93
23	Turners, etc.	165·0	66	59	80	78	90	31	81
25	Precision fitters, etc.	172·1	73	76	82	87	92	19	87
26	Machine erectors, etc.	410·2	109	108	103	105	117	14	111
29	Plumbers	72·7	90	74	85	92	103	29	94
33	Electrical fitters	59·3	112	126	136	131	138	26	133
34	Electricians	107·1	93	97	96	112	106	19	105
37	Welders, etc.	57·5	112	109	107	113	107	6	110
54	Carpenters, joiners	199·7	101	89	93	87	93	14	91
58	Builders, etc. labourers	135·6	117	153	174	146	139	57	145
59	Bricklayers	121·6	98	86	89	87	103	17	94
62	Other building, etc. workers	269·9	32	46	55	58	57	26	56
65	Other painters, etc.	221·9	104	99	103	104	108	9	106
72	Drivers of road vehicles	509·5	99	97	92	91	87	12	90
81	Salesmen, etc. (food goods)	68·0	64	72	77	87	78	23	79
107	Clerks, typists	780·2	82	94	105	110	98	28	101
108	Warehousemen, etc.	212·9	90	100	107	110	108	20	108
109	Crane, etc. drivers	102·0	157	106	107	93	93	64	96

*Occupations coded 041 and 042, whereas in Table 1, "Hewers and Getters" includes those coded 042 only.
†In Table 1, "Other Coalminers" includes coalminers, above ground, also.

of Yerushalmy (1951) weights the θs equally. These methods are equivalent, therefore, to the direct method and the "new" method, respectively, provided that the standardizing population is taken with an even distribution over the whole age range. They are not considered further below.

Most discussions on the measurement of mortality have been in terms of comparisons between districts, and methods based on the use of Life tables (see, for example, Benjamin, 1959) have been found suitable for some purposes. They are not considered here partly because they do not appear to have any major advantages for occupational comparisons but mainly in view of the conclusions of this study.

Reliability of the Measures

The standard errors given in Table 2 take account only of the variation in the numbers of deaths, *i.e.*, of the accuracy of the individual values of θ. They do not indicate at all the variation between the values of θ, which is seen in Table 3 to be considerable for both mining occupational groups. An index of this variation can be obtained from the range of the values of θ, that is, from the difference between the largest θ and the smallest θ. The S.M.R.s obtained by the four methods and the ranges of the θs are given below:

	Hewers and Getters	Other Coalminers
S.M.R. (direct)	157	96
S.M.R. (indirect)	153	96
S.M.R. (inverse)	132	105
S.M.R. (new method)	135	106
Range of θs	62	30

The S.M.R.s calculated by the two conventional methods will be essentially different from those calculated by the two newer methods unless either the age distributions of the deaths and of the population are similar or all the values of θ for one occupation are similar. The first of these situations used to arise when the population was much younger and the variation in death rates with ages much less marked: in 1851, these two factors operated to such an extent that the weights for use in the direct method would have been 11·8%, 20·9%, 21·0%, 21·9% and 24·4%. That the second of these situations arises only seldom is illustrated in Table 4. This gives the values of θ, taken from the Decennial Supplement (Registrar-General, 1958b) for all 22 occupational groups which had at least 50 deaths recorded in each age group (servicemen and policemen were not considered).

It can be seen that for most occupational groups the values of θ vary markedly with age: in only two groups is the range of the θs less than 10 and in just over a half of the occupations there are θs both below and above 100. It is of interest that in many occupations there is a pronounced age gradient.

Discussion

The present concept of occupational mortality is subject to fundamental objections which arise over selection and retirement; (see, for example, Reid (1959)). Any arduous job can only be performed by fit men and it seems inherently likely that such men, in their youth, will have more favourable mortality experience than men who are not fit enough to carry out such heavy work. Similarly,

the more arduous the job the earlier men must retire from it; coal-face work, for example, cannot be carried on at the same pace as formerly by men of over, say, 45. Such men may be employed in some lighter occupation, after retiring from their arduous work, until they die, and there is clearly a possible temptation both to these men when they complete Census schedules and to their widows registering their deaths, to record their earlier main occupation. That this led to serious inaccuracy in the assessment of mortality in mining occupations in 1951 has been shown by Heasman, Liddell, and Reid (1958). From their material it was clear that the greatest distortions occurred amongst the oldest age groups.*

It is thus clear that to assess occupational mortality by giving almost the entire weight to these groups will often lead to unreliable comparisons. Thus there is an important argument against the use of the conventional methods of standardization. The two newer methods (inverse and "new") are both better from this point of view. As in the "new" method the weights are determined by the age distribution in the population for all males and hence are standard for each occupation, the S.M.R.s obtained in this way are to be preferred to inverse S.M.R.s. The choice of method may, however, be governed largely by what information is available; for example, Kerridge (1958) suggested the use of the S.M.R. (inverse) where the age distribution in the occupation is unknown. Another factor of importance is the relative ease of computation.

A further possibility of improving the reliability of comparisons is to restrict still further the age range considered. Based on ages 20 to 54 the four methods produce S.M.R.s which are in much closer agreement. Even this, however, does not overcome the problems which arise over selection into the occupations: this might suggest curtailment at the younger end also, which would support Yule's (1934) comment that because there are so few deaths in the younger age groups, their inclusion can lead to serious inaccuracy. In any case, no single index can fail to be misleading in many cases. The American Public Health Association (1951) refers to "fantastic fallacies which may be inherent" when the conventional methods are used to compare mortality of populations with differing age distributions. Clearly, there is no way of describing in one term both the average of the relative death rates (θs) and their variation, which is usually considerable. It is therefore essential, as implied by Reid (1959) and many others, to examine each column of θs separately; although the newly proposed method of calculating an S.M.R. appears to be the most soundly based, neither it, nor any other single mortality index, should be used without a knowledge of the inadequacy inherent in it because of the variation in relative death rates.

*No allowance for these distortions has been made in the material discussed in this paper, which has been used purely for illustrative purposes

I would like to thank Mr. W. H. Leak for his great help in the preparation of this paper, Mr. D. Kerridge for his invaluable communication and Dr. J. S. McLintock for his helpful advice, and the referee for pointing out a number of errors and for his other useful comments.

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APPENDIX

The notation used is indicated in the table below:

Age Group	All Males			Particular Occupation		
	Population	Death Rates	Deaths	Population	Death Rates	Deaths
1 2 · · i ·	$P_i = \alpha_i P$	R_i	$X_i = \alpha_i P \cdot R_i$	$p_i = \beta_i p$	$r_i = \lambda_i \cdot R_i$	$x_i = \beta_i p \cdot \lambda_i R_i$
All	P	—	$\Sigma(X_i) = \Sigma(\alpha_i P \cdot R_i)$	p	—	$\Sigma(x_i) = \Sigma(\beta_i p \cdot \lambda_i R_i)$

Capitals are used for All Males, lower case letters for the particular occupation. The αs and βs give the proportions of the populations in each age group and so

$$\Sigma(\alpha_i) = 1 \; ; \; \Sigma(\beta_i) = 1 \; .$$

The ratios of the death rates (r_i) in the particular occupation to the death rates for all males in the same age groups (R_i) are λ_i. It is these values, expressed as percentages, which are quoted in columns (6) and (9) of Table 3, where they are called θs.

The S.M.R.s (expressed as ratios and not as percentages) calculated by the three methods are found to be:

$$\textit{Direct} \quad A = \frac{\Sigma(P_i r_i)}{\Sigma(X_i)} = \frac{\Sigma(\alpha_i P \cdot \lambda_i R_i)}{\Sigma(\alpha_i P . R_i)} = \frac{\Sigma(\alpha_i R_i \cdot \lambda_i)}{\Sigma(\alpha_i R_i)}$$

$$\textit{Indirect} \quad B = \frac{\Sigma(x_i)}{\Sigma(p_i R_i)} = \frac{\Sigma(\beta_i p \cdot \lambda_i R_i)}{\Sigma(\beta_i p \cdot R_i)} = \frac{\Sigma(\beta_i R_i \cdot \lambda_i)}{\Sigma(\beta_i R_i)}$$

$$\textit{Inverse} \quad C = \frac{\Sigma(x_i/R_i)}{p} = \frac{1}{p} \Sigma\left\{\frac{\beta_i p \cdot \lambda_i R_i}{R_i}\right\} = \Sigma(\beta_i \cdot \lambda_i)$$

and the fourth measure is defined as

"*New*" $D = \Sigma(\alpha_i \cdot \lambda_i)$.

Each of the four measures is seen to be a weighted mean of the λ_i. (When expressed as percentages, they are weighted means of the θs.) The weightings are according to

Direct	A: $\alpha_i R_i$	*i.e.*, according to deaths of All Males.
Indirect	B: $\beta_i R_i$	*i.e.*, according to expected deaths in the particular occupation.
Inverse	C: β_i	*i.e.*, according to the population in the particular occupation.
"*New*"	D: α_i	*i.e.*, according to the population of All Males.

On the usual assumptions (Registrar-General, 1958a; Kerridge, 1958) that (*a*) the number of deaths in each age group of the particular occupation is distributed with variance equal to mean and independently of the number of deaths in the other age groups and (*b*) the other terms (P_i, p_i, X_i and hence α_i, β_i, R_i) are based on such large numbers as to have effectively zero variance, we have

$$\text{var}(x_i) = x_i$$

i.e. $$\text{var}(\beta_i p \cdot \lambda_i R_i) = \beta_i p \cdot \lambda_i R_i \; .$$

Thus $$\text{var}(\lambda_i) = (\beta_i p \cdot \lambda_i R_i)/(\beta_i p R_i)^2 = \lambda_i/(\beta_i R_i p).$$

For any weighted mean $(\Sigma w_i \lambda_i)/(\Sigma w_i)$ of the λ_i in which the weights w_i obey the conditions assumed above

$$\text{var}\left\{\frac{\Sigma(w_i \lambda_i)}{\Sigma w_i}\right\} = \frac{\Sigma[w_i^2 \text{ var}(\lambda_i)]}{[\Sigma(w_i)]^2}$$

Hence the variances of the four measures are

$$\textit{Direct} \quad \text{var}(A) = \frac{1}{p} \frac{\Sigma(\alpha_i^2 R_i \lambda_i/\beta_i)}{[\Sigma(\alpha_i R_i)]^2}$$

$$\textit{Indirect} \quad \text{var}(B) = \frac{1}{p} \frac{\Sigma(\beta_i R_i \lambda_i)}{[\Sigma(\beta_i R_i)]^2}$$

$$\textit{Inverse} \quad \text{var}(C) = \frac{1}{p} \Sigma(\beta_i \lambda_i/R_i).$$

"*New*" $$\text{var}(D) = \frac{1}{p} \Sigma(\alpha_i^2 \lambda_i/\beta_i R_i).$$

A simple comparison of the variances is unrewarding, but in a number of cases it is possible to compare in terms of the squares of the coefficients of variation. In comparing the two conventional measures, direct (A) and indirect (B), we find

$$\left\{\frac{\text{C.V. (A)}}{\text{C.V. (B)}}\right\}^2 = \frac{\text{var(A)}}{A^2} \Big/ \frac{B^2}{\text{var (B)}} = \frac{\Sigma(\alpha_i^2 R_i \lambda_i/\beta_i) \; \Sigma(\beta_i R_i \lambda_i)}{[\Sigma(\alpha_i R_i \lambda_i)]^2}$$

on reduction, and this can be shown to be

$$= \frac{\text{A.M. } [(\alpha_i/\beta_i) \text{ weighted by } \alpha_i R_i \lambda_i]}{\text{H.M. } [(\alpha_i/\beta_i) \text{ weighted by } \alpha_i R_i \lambda_i]} \geqslant 1$$

Hence, the S.M.R (direct) has a higher coefficient of variation than the S.M.R. (indirect), except when all $\alpha_i = \beta_i$. If the age distribution of the particular occupation is similar to that of All Males, the ratio of the coefficients of variation will be close to unity.

It is also possible to compare the S.M.R. (inverse), C, with the S.M.R. (indirect), B. Here the ratio of the squares of the coefficients of variation reduces to

$$\left\{\frac{\text{C.V. (C)}}{\text{C.V. (B)}}\right\}^2 = \frac{\Sigma(\beta_i \lambda_i \cdot 1/R_i)}{\Sigma(\beta_i \lambda_i)} \Big/ \frac{\Sigma(\beta_i \lambda_i R_i)}{\Sigma(\beta_i \lambda_i)} = \frac{\text{A.M. } (R_i \text{ weighted by } \beta_i \lambda_i)}{\text{H.M. } (R_i \text{ weighted by } \beta_i \lambda_i)} \geqslant 1$$

Hence, the S.M.R. (inverse) has a higher coefficient of variation than the S.M.R. (indirect) unless all the death rates by ages for All Males, the R_i, are equal. Since these rates vary markedly (*cf.* column (4) of Table 1), the differences between their Arithmetic and Harmonic means will be considerable and so the two S.M.R.s can be expected to have noticeably different coefficients of variation. The ratios for Hewers and Getters and for Other Coalminers can be obtained from Table 2 as follows:

	Hewers and Getters	*Other Coalminers*
Direct compared with Indirect		
$\frac{\text{C.V. (A)}}{\text{C.V. (B)}}$	1·03	1·05
Inverse compared with Indirect		
$\frac{\text{C.V. (C)}}{\text{C.V. (B)}}$	1·56	1·59

The two lower ratios are very much smaller than that obtained from the data used by Kerridge. Here

$$\frac{\text{C.V. (C)}}{\text{C.V. (B)}} = \frac{6{\cdot}4}{74} \Big/ \frac{1{\cdot}4}{67} = 4{\cdot}1$$

and this high value is due to the wide variation between the R_i which arises because the age range is greater than is normally considered in occupational mortality comparisons.

Brit. J. industr. Med., 1960, **17**, 234.

OBSERVATIONS ON THE OCCUPATIONAL LIFE HISTORY OF THE COAL-FACE WORKER AT TWO COLLIERIES

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(RECEIVED FOR PUBLICATION OCTOBER 1, 1959)

Coal-face work is well known to be arduous and dangerous; it is performed in an unnatural environment even where conditions are good. Few men can continue this work until the age of retirement. They usually seek alternative employment either outside the industry or within the other major occupational groups at a colliery. The latter comprise the surface workers and those employed underground other than at the coal-face. This paper is concerned with those who stay within the industry. From a study of 73 workers who left the coal-face at two collieries, it indicates (1) the extent to which migration to alternative employment occurs each year, and (2) the resultant distribution of ex coal-face workers among these other occupational groups. The length of effective working life of the coal-miner on the coal-face, the reasons which precipitate his leaving it, and the type of work which he is able to do are also described. This information is of economic importance but it is mainly of value in assessing the effects of coal-face work upon the health of the coal-miner.

Annual Migration of Workers from the Coal-face

Sources of Information.—Information was derived from two collieries, A and B, whose main environmental features are indicated in Table 1. Both collieries are roughly the same depth. Colliery B has thinner seams and far less mechanical loading of the coal. It is also much warmer and subjectively the conditions are more unpleasant.

TABLE 1
MAIN ENVIRONMENTAL FEATURES OF THE COLLIERIES

	Colliery A	Colliery B
Total average number employed	1,725	1,637
Number of coal-face workers	706	806
Depth of shaft (yards)	750	716
Return air temperature (°F.):		
Dry bulb	74	79
Wet bulb	68	71
Type of mining	90% power loading	10% power loading
Seam thickness	Over 4ft.-6in.	2ft.-9in. upwards

Every coal-miner who, during the two years 1957 and 1958, was down-graded from the coal-face at Colliery A, and who, after six months, appeared unlikely to return, was interviewed. There were 34 such ex coal-face workers. Two who died while still working on the coal-face during this period, and about whom information was readily available, are also included in this group, making a total of 36.

Information of a similar group at Colliery B is presented for the year 1957. These numbered 33 which, with four deaths, provided another group of 37 ex coal-face workers. There is in all, therefore, a group of 73 coal-miners who have left the coal-face. Information in respect of the two groups is presented separately, but the emphasis is on the comparable results rather than on minor degrees of variance. Two collieries were used in order to preclude criticism that the results were a local phenomenon. For convenience the information about these 73 ex coal-face workers is expressed as rates per 1,000 coal-face workers.

Extent of Annual Migration from the Coal-face

In collieries A and B each year 2·7 coal-face workers from each 1,000 on the coal-face died whilst still working on the coal-face. 12·6 left the industry, but as some of these returned later and we have no evidence that they left the coal-face permanently, they are not included in the Tables.

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TABLE 2

NUMBER OF MEN LEAVING COAL-FACE PER ANNUM IN EACH AGE GROUP RELATED TO NUMBER AT RISK

Age Group	Collieries A and B			Colliery A			Colliery B		
	No. of Coal-face Workers per Annum	No. Leaving Coal-face per Annum	Rate per 1,000 per Annum	No. of Coal-face Workers per Annum	No. Leaving Coal-face per Annum	Rate per 1,000 per Annum	No. of Coal-face Workers per Annum	No. Leaving Coal-face per Annum	Rate per 1,000 per Annum
19-24	250	5	20·0	146	2	13·7	104	3	28·8
25-34	600	7	11·6	356	3	8·4	244	4	16·4
35-44	605	14	23·1	398	8	20·1	207	6	28·8
45-54	526	29	55·1	350	17	48·6	176	12	68·1
55-64	231	18	77·9	156	6	38·5	75	12	160·0
	2,212	*73	32·9	1,406	†36	25·5	806	‡37	45·9

*Includes six deaths on coal-face. †Includes two deaths. ‡Includes four deaths.

30·2 found alternative work within the industry, and we have information of their present work. For every coal-face worker, therefore, who is actually engaged on this work at the time of death each year, 11 others have found alternative work within the other major occupational groups in the industry, either on the surface or elsewhere underground.

Age of Workers on Leaving the Coal-face

Forty-seven of the 73 ex coal-face workers (64·4%) were over the age of 44, but these figures are best related to the number of coal-face workers in these age-groups. This is expressed in Table 2. Coal-face workers leave the coal-face at all ages (mean age 44·4 years). In the first five years (men aged 19-24) the rate is 20 per 1,000 employed there per annum. This falls to 11·6 for the next 10 years (men aged 25-34) and then the rate doubles to 23·1 for men in the 35-44 age group. For the next 10 years the rate increases by two and a half times to 55·1 per 1,000 and is then 77·9 per 1,000 over the age of 54. The coal-face worker over 34 is roughly three times more likely to leave the coal-face than the man under this age (44·7 and 14·1 per 1,000 per annum respectively). This emphasizes what one might expect—that coal-face work rejects unfit men at all ages, and more especially the older men.

Both collieries show this same general pattern. The overall rate at Colliery B is higher than that at Colliery A (45·9 and 25·5 per 1,000 respectively). This occurs at all age-groups and is most marked over the age of 54. This is due partly to the fact that coal-face conditions are much worse at Colliery B, but also to the fact that during 1957 10 extra posts as training supervisor were made available at this colliery owing to the development of a new training coal-face. These posts are lower paid than coal-face work, but slightly higher than work elsewhere underground. They are attractive and possibly half of the men who took these posts might otherwise have persevered for a little longer on the coal-face. Similar vacancies did not occur at Colliery A.

Number of Years Worked at the Coal-face by those Leaving the Coal-face

The number of years worked at the coal-face is closely related to the age at leaving the coal-face because most coal-face workers start at an early age. Sixty-nine per cent of the group under review were less than 24 years of age when they began work at the coal-face. Fig. 1 indicates the average life at the coal-face in each age-group of coal-miners leaving the face, and demonstrates this point.

The mean life at the coal-face of these 73 ex coal-face workers was 21·3 years, but some survived only a few years while the fittest endured 33·3 years. Those 47 who were over 44 years of age on leaving the face averaged 28·4 years of coal-face life, and the 26 aged less than 45 a coal-face life of 8·8 years.

Both collieries demonstrate the same trends, although the mean coal-face life at Colliery A was slightly longer than at Colliery B (21·8 and 21 years). In the younger age-groups, however, the average values are similar and the chief difference lies in the older men. Men can stay on the coal-face longer in mechanized mines. 36·5 years at Colliery A and 31·7 years at Colliery B were spent on the coal-face by those over 54; this was partly due to several men at Colliery B who might have stayed a little longer on the coal-face taking training supervisor jobs. As against this at Colliery A ex coal-face workers from neighbouring pits are usually recruited for these jobs, as the older coal-face workers find that they can continue longer on the mechanized coal-face.

Factors which Induce Coal-miners to Leave the Coal-face

Coal-miners tend to stay on the face as long as possible because of pride in their work in addition to its high status value and remuneration. Table 3 indicates the principal factors which cause men to leave the coal-face. It is not surprising that only 12 (16·4%) of the coal-face leavers admitted that the work was too much for them, or that they had had

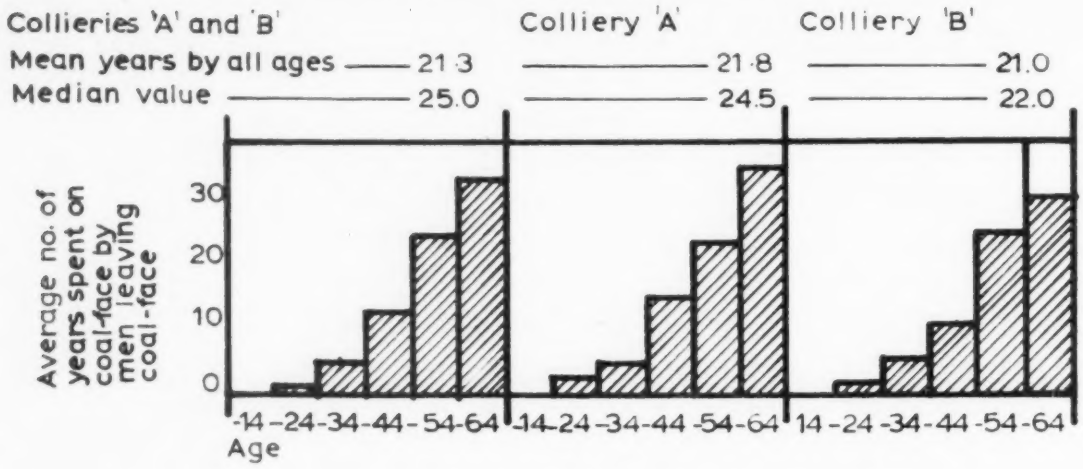
Collieries 'A' and 'B'
Colliery 'A'
Colliery 'B'
Mean years by all ages — 21·3 — 21·8 — 21·0
Median value — 25·0 — 24·5 — 22·0
Average no. of years spent on coal-face by men leaving coal-face
30
20
10
0
-14 -24 -34 -44 -54 -64
Age

FIG. 1.—Average number of years worked at the coal-face by men leaving the coal-face in each age group.

enough. Against this 30 (41·0%) complained of some incapacitating injury (over half of these were injuries to the back), and 25 (34·2%) of some debilitating illness. The injuries were distributed largely among the younger and the illnesses among the older men. Many had several disabilities, but the one which was thought to be the main factor is classified in Table 3.

TABLE 3

Main Factor Causing Men to Leave Coal-face	No. of Coal-face Workers	% of Total Leaving Coal-face
Injury	30	41·0
Illness	25	34·2
General fatigue	8	16·4
Voluntary	4	
Death	6	8·1
Total	73	99·7

Alternative Work Undertaken by Workers Leaving the Coal-face

Table 4 indicates the nature of the work which those coal-miners leaving the face are able to do. Only 20·5% are performing full-time road maintenance and development work. The trainee supervisors do this work on a part-time basis when there are no trainees, so that, in all, 35·6% may be said to be able to do moderately heavy work. Although this work is fairly severe on occasions, there is no rigid daily cycle of operation as there is on the coal-face. Many explain that it is the speed of coal-face work which proved so exacting. Over half, however (52·0%) were able to do only the lightest of work such as conveyor operator (button job), belt patrol, engine driver or loco driver. A few men find their way to the surface, usually, as general labourers in the yard gang. Surface work is not generally popular with the underground worker. Twenty find alternative work underground for each one going to the surface. Apart from the reduced wages the underground worker misses the companionship of men of similar ilk, for surface work attracts a vastly different type of man.

TABLE 4

Nature of Alternative Work	No. of Men	% of Total
Trainee supervisor	11	15·1
Road maintenance and development	15	20·5
Light work	38	52·0
Surface—General labourer (light work)	3	4·1
(Deceased)	(6)	(8·1)
Total	73	99·8

Distribution of Ex Coal-face Workers Among Others Underground and Surface Workers

As 30·2 from every 1,000 coal-face workers each year found alternative employment among "others underground" and "surface workers", there will be an accumulation over the years of ex coal-face workers in these latter occupational groups. This has been shown by the examination of a random selection of 46 "others underground" and 26 "surface workers" at Colliery A (Edmonds, 1958). Twenty-five of the former (54·5%) and six of the latter (23·0%) were found to have done some coal-face work. They form a larger proportion of "others underground" in the older age groups—77·7% of those over the age of 44.

Fig. 2 indicates the number with and without coal-face experience in the different age groups of

the random selection of 46 "others underground", and demonstrates the increasing proportion of the former in the higher age-groups.

This distribution raises a secondary point, namely, whether by selective recruitment more jobs could be made available for ex coal-face workers in these occupational groups. Among the 46 "others underground", 21 had no coal-face experience. Only six of these, however, were doing jobs for which the ex coal-face worker would be suited; the rest were craftsmen. It would seem, therefore, that only six out of 46 (or 13%) more jobs among "others underground" could be made available. On the surface, colliery managers expressed surprise that 23% were ex coal-face workers since recruitment to the surface is for the most part direct. It is not by any means a source of alternative work for underground workers, as in general they dislike surface work.

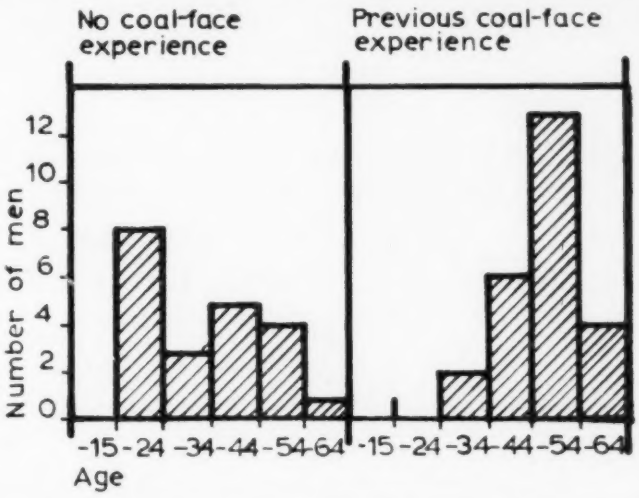

FIG. 2.—Random sample of "others underground" at Colliery A showing previous coal-face experience.

The distribution of ex coal-face workers amongst "others underground" and on the "surface" indicates the cumulative effect of movement from the coal-face in the past. Such a group is not representative of the total coal-face workers who seek alternative work in the industry each year. These are of all ages initially, but those who left the coal-face at an early age will tend to outnumber those who left later, for the latter proportionately retire and die more quickly.

Analysis of this group of 31 ex coal-face workers in the random selection confirms this; 22 (70·9%) had left the coal-face before reaching 45 years of age and their average coal-face life was 16·1 years as would be expected. Injury or illness was the main cause of their leaving the coal-face in 87·0% and only six (19·4%) were still able to perform tasks other than light work. These 31 ex coal-face workers, therefore, closely resemble those younger men who leave the coal-face each year.

Discussion of Results

Heasman, Liddell, and Reid (1958) analysed the actual occupation at death (which they verified with great thoroughness) of a group of coal-miners. They noted that the mortality ratio for coal-face work was less than that of the coal-miner employed elsewhere underground; they suggested that only a man of good physique undertakes coal-face work, and that if he should become unfit he would be expected to move to lighter work. This limited survey endorses this explanation and shows that for every coal-face worker who dies while employed on the coal-face, 11 transfer to other jobs, mostly elsewhere underground. The majority of these are over 44 years of age and are suffering from some illness or injury. The lower mortality rate for coal-face workers is therefore a measure of a robust body of coal-miners who are still able to endure the rigours of coal-face work. The rates for other workers underground may, in fact, reflect the effects of such rigours, for a large proportion of these men have experienced many years at the coal-face. It is suggested, therefore, that useful information about the health hazards of coal-face work might be obtained by a study of other underground workers.

Conversely, it is usual, during investigation, to classify the main occupational groups at a colliery as "coal-face workers", "others underground" and "surface workers" as if they were separate entities. This is satisfactory where the matter pursued is a direct result of the immediate environment, but where previous conditions may be important then the past occupational history must be considered, for example in studies of the prevalence of osteoarthritis of knees and spine.

We should like to thank Dr. Trefor Watkins for his friendly help and guidance throughout this investigation.

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THE ASSESSMENT OF ELECTROENCEPHALOGRAPHIC CHANGES AND MEMORY DISTURBANCES IN ACUTE INTOXICATIONS WITH INDUSTRIAL POISONS

BY

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(RECEIVED FOR PUBLICATION JUNE 25, 1959)

A report is given of the results of the electroencephalogram (EEG) and of an experimental memory examination in a group of 22 cases of acute carbon monoxide and solvents poisoning of varying severity. An abnormal EEG recording, most often in the form of theta activity 5-6 sec., was found in 12 patients; memory disturbances were found in 13 cases. There was correlation between the results of the two examinations as well as with the clinical classification of the degree of intoxication. The methods are suitable for the solving of various theoretical and practical questions in industrial toxicology.

There is a need for methods of objective assessment of changes brought about in the central nervous system by toxic substances. A measure of the depth and extent of any injury would be of great importance in measuring disability. We have, therefore, tried to follow the signs of disturbances in the central nervous system due to industrial poisoning with the help of the electroencephalogram (EEG) and an experimental memory test.

EEG changes in acute carbon monoxide poisoning have received a good deal of attention and it is generally agreed that on recovery of consciousness the EEG returns to normal after the patient has recovered clinically (Noel, 1955).

Massman (1955) noted persistence of EEG changes for three weeks after intoxication; Noel (1955) found that the speed of the waves was inversely proportional to the degree of intoxication. The literature on poisoning by solvents is less extensive. Klimková-Deutschová and Lesný (1957) followed up cases of methyl chloride poisoning and found a relation between EEG changes and the clinical condition of the patient. Nissen (1953) described a case of acute trichloroethylene poisoning with evidence of an extrapyramidal lesion which was accompanied by slow EEG rhythm persisting for 15 months. Anderson (1957) found EEG changes in the form of theta waves in six out of 29 cases of chronic exposure to high concentrations of trichloroethylene. She was not convinced that the changes were related to poisoning even though in some cases the EEG returned to normal after the patient stopped working with trichloroethylene.

Disturbances of recall persisting for several months after carbon monoxide poisoning have been reported (Shillito, Drinker, and Shaughnessy, 1936; Störring, 1936 and Jéquier and Guerdjikoff, 1956). Defects of memory were noted in 38% of people chronically exposed to trichloroethylene (Grandjean, Münchinger, Turrian, Haas, Knoepfel, and Rosenmund, 1955) and have been found after methylchloride poisoning (Petráň, 1955). Pathological changes in the brain are well known after carbon monoxide poisoning and have been reported in rabbits after acute trichloroethylene poisoning (Bernardi, Penzani, and Luvoni, 1956).

Cases Studied and Methods Applied

We have examined 22 cases of acute poisoning by carbon monoxide and industrial solvents with an average age of 38 years. Of 12 cases of carbon monoxide poisoning nine were from illuminating gas and three from oven smoke. Of the solvents, trichloroethylene was the cause in six cases, methyl chloride in two and one each from methyl bromide and acetone. Eighteen of the cases were accidental (12 at home; six at work) and four were attempted suicides.

The patients were examined clinically from the

medical, psychological and psychiatric aspects; the EEG examination was conducted on a 16-lead instrument (Kaiser) with the application of hyperventilation and photostimulation.

In the experimental examination of memory disturbances we applied a method used in our previous paper (Chalupa, 1958) to a population of 120 people including those with acute intoxication with various industrial poisons, chronic intoxication, a control group of normal persons and a group of persons with organic brain damage. Briefly the method consists of (*a*) the assessment of spontaneous reproduction of 20 words recited from a list; (*b*) recognition of the same material interspersed with 10 new items of control; (*c*) reproduction of 30 word pairs, the two words standing in some relation to each other (window—light, injury—pain).

All items are presented acoustically.

Our rationale was that not all memory components are injured to the same degree through exposure to the toxic agent, so that it should be possible to differentiate pathological changes from natural inter-individual variations in memory performances. The average interval from the date of intoxication to the date of examination was three days (one to nine). At that time disturbances of consciousness had passed. The EEG examination followed on the next day.

The further examination depended upon the category of poisoning (light, moderate or severe) into which the patient had been placed. This depended on the concentration of the noxious agent, duration of exposure, the incidence and duration of unconsciousness, the clinical condition on admission, laboratory findings and course of recovery.

Results

EEG pathological changes were composed of middle voltage theta activity of 5-6 sec. of a rather regular type. The pattern was diffuse in three cases, localized in five. The theta activity was reflected in episodes localized into the anterior or posterior part of the brain in four cases; very rarely was it generalized. Episodes were more frequently found after hyperventilation or photostimulation. Generalized polymorphic dysrhythmia delta 2-3 sec. and theta 4-5 sec., with absence of normal rhythms, was found in one case only. The distribution of the EEG findings can be seen in Table 1.

Comparison of the EEG findings and the clinical classification shows a significant correlation. Of the mild cases five EEG's were normal and one atypical, but none was abnormal. Of the moderately severe cases three (Nos. 7, 9 and 10) had normal EEG's and all of these were cases of carbon monoxide poisoning with less than three hours of unconsciousness. One (No. 21) of the severely poisoned cases had a normal EEG. This was an obese young girl poisoned with trichloroethylene and benzene.

TABLE 1

DISTRIBUTION OF THE EEG FINDINGS

Finding	No. of Cases
I. Normal	9
II. Atypical	1
III. Slightly abnormal	2
IV. Abnormal	9
V. Severely pathological	1

The average values of the memory tests in the acute intoxication cases compared with the control group of healthy persons show disturbances of logical memory and decrease of accordance in recognition, while the least injury was suffered by the mechanical memory (Table 2). The reproductive tendency and the percentage of false reproductions in the recognition test was, on the contrary, increased. This is in accordance with previous findings in acute intoxication.

The changed relations of various memory components suggest also the presence of a pathological process in individual cases. The comparison is undertaken with the help of a standard scale constructed from average values and standard deviations in a large population. We evaluated five pathognostic signs (the quantitative prevalence of reproductive tendency over the logical memory, over the accordance of recognition, over mechanical memory; prevalence of mechanical memory over logical memory; occurrence of false reproductions) whose frequency in the groups examined is shown in Table 3.

The results of the various examinations conducted are given in Table 4. Taking into account the

TABLE 2

AVERAGE VALUES OF THE VARIOUS MEMORY COMPONENTS

Group	Age	Logical Memory	Accordance in Recognition %	Mechanical Memory	Reproductive Tendency %	False Reproduction %
Acute intoxication (22 cases)	38·05	9·5	53·9	5·7	39·8	12·7
Normal persons (20 cases)	36·1	13·0	64·5	6·3	36·25	4·0

TABLE 3

RESULTS OF THE MEMORY EXAMINATION BY THE GENERAL CLASSIFICATION

Number of Pathognostic Signs	0	1	2	3	4	5
Acute intoxication (22 cases)	2	3	4	8	5	—
Normal persons (20 cases)	8	6	6	—	—	—

variations in normal population we regard the findings in nine persons examined as within normal limits, while 13 are pathological. Memory disturbances increase with the degree of clinical intoxication. Contrary to the EEG findings some of the mild intoxications had memory disturbances (Cases 4 and 6), otherwise the same is valid for the EEG in comparison with clinical criteria, namely that carbon monoxide intoxication with a short period of unconsciousness was not necessarily followed by pathological changes when adequately treated (Cases 7, 9 and 10). We had one case of a severe peroral trichloroethylene intoxication with a long period of unconsciousness without memory disturbance (Case 22).

Notwithstanding certain differences, general accord can be found between the EEG findings and the memory examination in acute intoxications (Table 5). Differences were found in four cases, two patients with mild intoxication (Cases 4 and 6) who had memory disturbance but a normal EEG and two patients with severe intoxication (Cases 21 and 22) who had either normal EEG and abnormal memory examination or *vice versa*.

TABLE 5

COMPARISON OF THE EEG FINDINGS AND THE RESULTS OF THE MEMORY EXAMINATION WITH THE CLINICAL CLASSIFICATION OF THE DEGREE OF INTOXICATION

	EEG Examination Pathological Findings	Memory Examination Pathological Findings
Mild intoxication (6 cases)	0	2
Moderate intoxication (10 cases)	7	6
Severe intoxication (6 cases)	5	5
Total (22 cases)	12	13

Of the patients with a pathological EEG, 83% had memory disturbances, whereas for patients with normal EEG the figure was 30%. The coefficient between the two findings is $r = +0{\cdot}472 \pm 0{\cdot}112$ which is four times the standard deviation and therefore statistically significant. While the agreement between the two examinations seems assured, in practice the methods will support each other.

In view of the small number of cases investigated, the statistical treatment of sub-divisions according to toxic substance would present difficulties. On the whole it would seem from our material that the relations between the degree of intoxication, EEG recording, and degree of memory disturbance are

TABLE 4

RESULTS OF VARIOUS EXAMINATIONS CONDUCTED IN CASES OF ACUTE INTOXICATION

Case No.	Age	Sex	Toxic Agent	Mode of Assimilation	Nature of Accident	Loss of Consciousness	Degree of Intoxication	EEG Classification (Table 1)	Memory Disturbance Classification (Table 3)	Clinical Sequelae
1	51	M	Carbon monoxide	Inhalation	Home accident	No	Mild	I	0	0
2	16	M	Carbon monoxide	Inhalation	Home accident	No	Mild	I	2	0
3	72	F	Carbon monoxide	Inhalation	Home accident	No	Mild	II	1	0
4	36	F	Carbon monoxide	Inhalation	Home accident	No	Mild	I	4	0
5	57	M	Trichloroethylene	Ingestion	Home accident	No	Mild	I	1	0
6	19	M	Acetone	Inhalation	Industrial	No	Mild	I	4	0
7	49	F	Carbon monoxide	Inhalation	Suicidal	Yes	Moderate	I	2	0
8	18	F	Carbon monoxide	Inhalation	Suicidal	Yes	Moderate	IV	3	0
9	21	F	Carbon monoxide	Inhalation	Home accident	Yes	Moderate	I	0	0
10	24	M	Carbon monoxide	Inhalation	Home accident	Yes	Moderate	I	1	0
11	30	M	Trichloroethylene	Ingestion	Home accident	No	Moderate	IV	3	0
12	22	F	Trichloroethylene	Ingestion	Home accident	No	Moderate	IV	4	+
13	35	M	Trichloroethylene	Inhalation	Industrial	Yes	Moderate	III	2	+
14	47	M	Methylchloride	Inhalation	Industrial	No	Moderate	IV	3	+
15	40	M	Methylchloride	Inhalation	Industrial	No	Moderate	IV	3	+
16	51	M	Methylbromide	Inhalation	Industrial	No	Moderate	III	3	+ +
17	40	M	Carbon monoxide	Inhalation	Suicidal	Yes	Severe	IV	3	0
18	17	M	Carbon monoxide	Inhalation	Home accident	Yes	Severe	IV	3	0
19	57	F	Carbon monoxide	Inhalation	Home accident	Yes	Severe	V	3	death on 32nd day
20	54	M	Carbon monoxide	Inhalation	Industrial	Yes	Severe	IV	4	+ +
21	19	F	Trichloroethylene	Ingestion	Suicidal	Yes	Severe	I	4	+
22	62	M	Trichloroethylene	Ingestion	Home accident	Yes	Severe	IV	2	0

Note.—Sequelae of intoxication:
+ = minor passing post-intoxication symptomatology (headache, vertigo, insomnia).
+ + = lasting sequelae of organic character.

more pronounced in carbon monoxide than in the solvent intoxications. Further investigations in this respect are in progress.

The solvent intoxications, as measured by our two examinations, are more severe than those by carbon monoxide, which is rather surprising in view of the fact that they were followed by loss of consciousness in three cases only, while it occurred in eight of the carbon monoxide intoxications. This is striking in the moderate group, where among four carbon monoxide intoxications only one EEG finding was abnormal, while the six solvent cases all had abnormal EEG values. Pathological EEG findings occur as a rule in severe carbon monoxide intoxication with a high concentration of the noxious agent and a long sojourn in it. Memory disturbances follow the same pattern.

Quantitative differences in the findings in our group may be explained mostly by efficient and early hospital care in the acute carbon monoxide intoxications, in contrast to the prolonged noxious effects in the cases of solvent poisoning. Qualitative differences could not be ascertained, which is reflected in the consistency of the central nervous system injury by various noxious agents.

No constant relation was found between the EEG and memory examinations on the one hand and the loss of consciousness on the other; this is understandable when we consider the severe solvent intoxications which rarely led to loss of consciousness. The time of exposure seems to be of more importance, as pathological findings were more numerous with prolonged exposure.

Most patients recovered clinically within a week, a fortnight being exceptional. One patient (Case 19) died on the 32nd day after a period of temporary improvement between the fifth and 10th day. Serious clinical sequelae were found in two patients (Cases 16 and 20), whose working ability was affected. Minor sequelae followed in five patients.

Follow-up EEG examinations did not show any improvement in some cases for as long as a year after the clinical picture had become normal. This persistence of abnormal findings is described in the literature on carbon monoxide, but less so in solvents intoxication.

The memory tests were repeated while using new material of equal value. Results showed improvement of the logical memory and of recognition, the mechanical memory did not improve.

Neurological findings were mostly normal in the solvents intoxication while some were pathological in the carbon monoxide group.

Conclusion

Electroencephalography and the experimental memory tests may be of value in the assessment of the degree of intoxication and of the eventual sequelae when treating injuries from carbon monoxide, trichloroethylene, methylchloride, methylbromide and other toxic agents met with in industry. The methods were very sensitive and hence well suited for the solving of theoretical and practical questions of industrial toxicology, where an objective evaluation of injuries to the central nervous system is required.

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BOOK REVIEWS

A Doctor's Approach to Industrial Medicine. By H. P. Dastur. (Pp. 151.) Bombay: Tata Institute of Social Sciences. 1960.

This small book, made up in the main of chapters already published as articles in various journals, is the quintessence of a lifetime's experience of industrial medicine in India. As the vast sub-continent has in a relatively short span of years taken a number of rapid strides from being a poor agricultural community towards that of a modern industrial economy, so our own problems of the past two hundred years, are being recapitulated and intensified. To them the author has brought the results of Western experience modified by a mind steeped in Eastern philosophy and religion.

Dr. Dastur realizes the convenience of studying a particular function of the mind or body or social group in isolation, but rebels against a way of life from which is absent "any serious attempt at an approach to the concept of the wholeness of life". He propounds no system but implicit in these pages is this philosophic approach.

Since the end of the war he has visited Europe on three occasions. The many friends he made here and his colleagues in India will be glad to have this slim volume to peruse at leisure and recollect at work.

J. A. SMILEY

Medical Surveys and Clinical Trials. Edited by L. J. Witts. (Pp. x + 328. 35*s*.) London: Oxford University Press. 1959.

Doctors who serve industry often wish to undertake research. A few make the attempt. Others content themselves with providing a field for full-time research workers. To undertake research in addition to a full-time appointment means many hours of labour in "leisure" time and the research-minded industrial physician naturally envies the full-time research worker in this respect. All research involves Churchill's tetralogy of "blood, sweat, . . .", but a fine impression of the needs can be obtained from this book. Perhaps the necessity of consulting the statistician first is not sufficiently emphasized, but otherwise the studies of methodology are magnificent. The chapters on prevalence surveys, retrospective and prospective studies, and follow-up studies are particularly useful. So is the chapter with the intriguing title "Volunteers, Controls, Placebos, and Questionaries". The second part of the book gives practical examples in, *inter alia*, chest and cardiovascular diseases, mental illness, cancer, and diseases of the joints. The 18 contributors are well known and superb in their respective fields. Research workers will pore over the parts of this book that interest them: industrial physicians who have a mind to undertake a piece of research would be well advised to browse slowly through it, for here are clearly-expressed help and encouragement.

L. G. NORMAN

Principles of Disability Evaluation. By Wilmer Cauthorn Smith. (Pp. xiii + 210. 56*s*.) Philadelphia and Montreal: J. B. Lippincott; London: Pitman Medical Publishing Company. 1959.

Dr. Smith is Chief Medical Advisor to the Oregon State Industrial Accident Commission and obviously has wide experience in the field of disability evaluation. He has endeavoured—and to a large extent succeeded—to show how to apply logic to a problem which is so frequently distorted by the emotion of both patient and physician.

This work contains many useful hints for the medical witness in court, and Dr. Smith's advice on compiling a medico-legal report would receive the wholehearted approval of the legal profession.

The nature of disability is discussed only in relation to the capacity "to have and to hold" employment. Within these limits this section is excellent. The vicious triad—excessive sickness absence, excessive treatment, and excessive examination—is ably treated. The proving of relationship between accident and medical condition is ably expounded.

Physicians who regularly undertake medico-legal reporting in "compensation" cases will readily agree with many of Dr. Smith's observations and principles, and will find this work of value if only in confirming them in their opinions. I would recommend this book to those who venture intermittently into the field, though they may find the literary style somewhat ponderous.

J. L. FYFE

Diabetes en Arbeid. By E. H. W. Wijnmalen. Foreword by Prof. P. Muntendam. (Pp. 171. H. g. 9·50.) Assen. Netherlands: Van Gorcum. 1959.

Dr. Wijnmalen set out to assess the ability of diabetics to perform work. Replies to a questionnaire from industrial medical officers in the Netherlands showed that, for diabetics, general opinion was against irregular and shift work and work involving heavy or irregular exertion or in which loss of consciousness involves danger to the patient or others.

Sickness-absence data were obtained from three employers, for diabetics and for all employees. There was

no significant difference in the inception rates but diabetics tended to have longer absences. Stabilization of the diabetes caused only a small part of the absence.

These results, with detailed individual information, indicate that diabetics present no special problem in several occupations and many are capable of heavy work, even outside normal shifts. But stabilization difficulties cause problems and the combination of diabetes with another condition may be disabling.

This valuable study is based on limited data and shows the need for further work, including "prospective" surveys. It also suggests the possibility of similar studies of other conditions.

C. J. CORNWALL

Work and the Heart. By 93 authors, edited by Francis F. Rosenbaum and Elston L. Belknap. (Pp. xxii + 537; illustrated. $12.00.) New York: Paul B. Hoeber. 1959.

This book is an account, running into more than 500 pages, of the first Wisconsin Conference on work and the heart which was held in May, 1957. The 93 participants include many Americans who have made their name in cardiology and circulatory and exercise physiology; also Professors A. C. Burton, J. D. Hamilton and J. C. Paterson from Canada, Dr. A. Morgan Jones from Manchester, and Drs. G. Biörck, M. J. Karvonen and H. H. Weber from Scandinavia and Germany. The conference was subdivided into five sections, meeting concurrently, which, between them, covered the basic and clinical physiology, pathology, re-employment, and workmen's compensation.

The book opens with a series of lucid articles describing basic cardiac physiology; these include the physics and biochemistry of muscular contraction and, from Dr. S. J. Sarnoff, an account of the oxygen consumption of the heart in relation to cardiac work and to factors affecting the coronary circulation. These are followed by chapters discussing cardiac activity in normal subjects, including coronary blood flow, the control of cardiac output, the regulation of heart rate (Dr. D. B. Dill), the effect of age (Dr. Milton Landowne), and of strenuous exercise (Dr. M. J. Karvonen). The assessment of cardiac efficiency is considered in relation to the strain to which the heart is subjected as a result of exercise; that arising out of emotional and thermal stress, and the additional effects of dilatation and cardiac failure. The need for better standardization of tests of fitness emerges clearly from this section of the proceedings.

The aetiology of coronary disease is considered by Drs. Ancel Keys and H. L. Taylor in relation to occupation and to physical activity insofar as these affect the serum cholesterol concentration. Dietary fat intake is mentioned briefly but not the possible prophylactic value of unsaturated fatty acids. The role of capillary haemorrhage and thrombosis is discussed in the section on pathology, as is the part played by physical and emotional stress in precipitating coronary occlusion. The significance of silent myocardial infarction and, in fatal infarctions, the common absence of coronary occlusion are also treated.

One section of the book is devoted to a consideration of re-employment of cardiac patients, including both suitability of jobs and employment record, and also the effect of employment on the course of the disease. This section, which will be of particular interest to industrial medical officers, includes accounts of cardiological experience in several industries and work situations as well as of the 35 work classification units in the United States, which have been set up to solve these problems. The place of these special diagnostic and rehabilitation units in the framework of the general medical and rehabilitation services of the community is discussed constructively.

The last section on workmen's compensation in relation to cardiovascular diseases in the United States includes both medical and legal viewpoints.

This brief survey indicates the range of subject matter covered by this large, well-produced book. Some of the individual contributions are in fact reviews; the majority are individual viewpoints. To one who is a physiologist, the first two sections in particular are immensely stimulating and the book should provide a valuable jumping off point for anyone interested in exploring further this fascinating field. Inevitably the picture they acquire will be out of date in some places and biased or incomplete in others, but with several hundred references to assist them they are unlikely to go badly astray. One reference which might be added is "Cardiac Control" by R. F. Rushmer and A. O. Smith (*Physiol. Rev.*, 1959, **39**, 41). The conference promises to be followed by others in which current trends will be critically assessed; meanwhile the proceedings of this first conference can be recommended.

J. E. COTES

The Health of Business Executives. The Transactions of a One-Day Conference held in the Royal Festival Hall, London (November 20, 1959). (Pp. 126.) London: The Chest and Heart Association. 1960.

In November 1959 nearly 500 directors spent a day trying to find out how to avoid a premature death from an excess of work, travel, food, drink, and (all be they self-administered), drugs. Over 100 doctors attended the same conference, no doubt seeking, if not a new elixir, a fresh means of dispensing the elixir of life to directors.

For the doctors, there was no new elixir. For the directors, there was no primrose path, but some contributions, notably Sir Stanley Davidson's "Overweight and Diet", were models of how to present medical matters to the layman.

Business men deal with facts; philosophers with fancies. One of the difficulties facing the doctor who seeks to be a philosopher and friend to his executive is to find the right mixture of facts and fancies. It so often becomes a series of cautionary tales about "patients I have known". Sir Stanley's contribution summarizes excellently the theme which creeps into practically every contribution, namely, that the greatest hazard of living today is to be overweight, and this is by no means a health hazard that is confined to the executive.

Mr. Beric Wright's rules for travellers suggest a suitable topic for any management conference, and a pamphlet on this theme would be helpful—perhaps one is already available?

Few would agree with the views of Mr. Dickson Wright, a surgeon, who is out of sympathy with the contribution that medicine makes to industry and commerce, albeit they have been expressed forcibly, and for this reason if none other, this pocket-size booklet should be read by all industrial medical officers.

J. C. GRAHAM.

Detoxication Mechanisms. The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds, 2nd ed. By R. Tecwyn Williams. (Pp. x + 796. 126*s*.) London: Chapman & Hall. 1959.

The first edition of this book, less than a third of the weight of this volume, was packed with useful information. The ratio of information to mass remains the same and the style of the new edition does not depart materially from that of the original one. The work is essentially a book of reference and is more of a dictionary than a discussion. Anyone who wishes to try to understand the mode of action of a foreign chemical that may be ingested either as a drug or in food or during occupational exposure should start by referring to this volume. With an excellent index and references at the end of each chapter, the original information is easy to trace. It is a book of chemistry and the subject is one which owes much to the work of the author and his colleagues. The occasional references to medicine and statements such as "organic nitrites . . . have been used for many years in the treatment of hypertension" or "menthol . . . is a compound of great importance in medicine" or that "synthalin is used in diabetes" do not enhance the value of the chemical information provided. Problems of industrial toxicology are not enlarged upon. The metabolism of benzene is fully discussed but no reference is made to its unique toxicity to the bone marrow of mammals when compared with related aromatic hydrocarbons. The toxicity of benzene and chlorobenzene are compared only on the basis of their narcotic action (p. 251).

Although documentation is on the whole excellent there are occasional gaps such as the metabolism of cyclohexylamine (p. 119) and there is no reference for the statement that vitamin B_1 relieves the poisonous effects of carbon disulphide (p. 40).

Having completed this masterly compilation the author might consider a smaller volume discussing the significance of the information he has presented. A single chapter at the end stimulates the appetite for more. Thus the enzyme systems in liver are mentioned briefly in many places but no general account is given of the ability of the liver to transform foreign chemicals reaching it. For technical reasons the rabbit or larger species has been used in work on the excretion of metabolites yet most toxicity testing is done on rats or mice. There is probably enough information now available to make some useful generalization on species differences. Much of this work described so far has been of necessity done on chemicals that may be administered in relatively large quantities. Refined methods for the isolation, purification, and identification of chemicals will enable more work in the future to be done on more toxic drugs and chemicals.

It seems probable that further editions of this book will be called for at much shorter intervals than the 12 years that separate the first from the second edition.

J. M. BARNES

Recherches sur la Toxicologie du Thallium. By René Truhaut; Foreword by René Fabre. (Pp. 272; 54 figures.) Paris: Institut National de Sécurité pour la Prévention des Accidents du Travail et des Maladies Professionnelles. 1958.

This is a more complete study than any hitherto on the mechanism of thallium poisoning. Previous reports and theories are fully cited. The author stresses the importance of covering the different fields of analytical chemistry, biochemistry, physiology, and cytology when attempting to penetrate the mechanism of action of toxic substances. This monograph is thus divided into five parts incorporating experimental results obtained under these headings. A survey of this nature tends to be superficial in many respects. However, the spectrophotometric method described for measuring thallium in biological media, the data on distribution of thallium in animals together with those obtained using radioactive thallium are very valuable.

Among the many and varied investigations made, the section on the appearance of alopecia in animals suffering from thallium poisoning is the most striking. Contrary to some earlier reports thallium was found to be without effect on the thyroid in spite of an accumulation of the metal in this organ.

Of the substances tested to alleviate thallium poisoning certain sulphur-containing amino- acids showed some degree of efficiency while B.A.L. was without effect.

From results in the more biochemical and pharmacological sections no mode of action is, or can be, suggested for thallium poisoning. In fact, the author concludes that the mechanism of the toxicity of thallium is as equally complex as the chemical properties of the metal, termed "métal paradoxal" by early workers.

J. E. CREMER

Bibliography of Cancer Produced by Pure Chemical Compounds. A Survey of the literature up to and including 1947. By Otto Neubauer. (Pp. xxvii + 604. 42*s*.) London: Oxford University Press. 1959.

All cancer workers will welcome this compilation of the literature starting from the first induction of tumours by a pure chemical compound by Kennaway, in 1930, using 1 : 2 : 5 : 6-dibenzanthracene (considered at the time to be the 1 : 2 : 7 : 8-dibenzanthracene).

The value of such a bibliography depends on its reliability, completeness, and ease of perusal. Though

the author stresses that absolute completeness has not been attempted, yet the coverage is impressive. The material was collected from 480 journals and other publications, listed on pp. xi-xx.

The relation of arsenic to cancer already reported by Professor Neubauer in a bibliography (*Brit. J. Cancer*, 1947, **1**, 192-251) is excluded. Papers dealing with the carcinogenic action of ultra-violet and sunlight are included, but not those dealing with other ionizing radiation.

The material is listed in two parts, consisting of (1) an authors' index in alphabetical order, 270 pages, and (2) a subject index, 326 pages, divided into 32 sections, each comprising several subsections. Each entry consists of the names and initials of all the authors, the name, volume, and page of the periodical and the year of publication, full title in the original language (except when this is printed in Japanese or Cyrillic characters) and its English translation.

There is a key (pp. xxi-xxvii) to the arrangement of the subject index in the various sections dealing with individual aspects of the carcinogens, their physical, chemical, and biological properties, metabolism, modes of administration, local and systemic effects in various species, including man, the influence of intrinsic and extrinsic factors. The subsections deal with the particular classes of the carcinogens, polycyclic compounds, azo compounds, acetaminofluorene, aromatic amines, sterols, and so on. A valuable feature is the collection of general reviews in section 31.

This bibliography allows a quick survey of the older literature on any particular aspect of carcinogenesis with chemical compounds, and it is to be hoped that it will be followed on similar lines by subsequent volumes on the literature published since 1947.

The criteria by which the author selected the "pure chemical carcinogens" appear rather arbitrary. Thus, papers dealing with heated fats and cholesterol are included, but not all those dealing with carcinogenic fractions of tar. However, with such a diffuse and complicated subject as carcinogenesis the problem of selection is extremely difficult.

It is sad that neither the author, nor Sir Ernest Kennaway, who suggested the compilation of this bibliography and helped to secure financial support for it, first from the Donner Foundation and since 1947 from the British Empire Cancer Campaign, lived to see the completed work. The completion of the final stages of this book is due to Miss Phyllis M. Coombs, of the library staff of the Chester Beatty Research Institute.

R. SCHOENTAL

Harmful Effects of Ionising Radiations. By Ethel Browning. (Pp. xii + 158; 5 figures. 15*s*.) Elsevier Publishing Co. Amsterdam, 1959. London: D. van Nostrand. 1960.

There should be a great demand for a small book of this size on this subject. The number of people—industrial medical officers, health physicists, safety officers, executives—with a need to know the basic principles must be multiplying rapidly with the increasing use of ionising radiations and radioactive materials.

No single person, one would have guessed, would have been more fitted to be the scribe than Dr. Ethel Browning, who is so widely respected by the medical profession and by "industry" for her guidance over nearly a generation as H.M. Medical Inspector of Factories and for her personal researches in this field. Nevertheless, to the reviewer the material presented has characteristics in common with the curate's egg. The good bits are where the author is definitely discussing her own field—the observed clinical features of men and women, who in the past were for one reason or another over-exposed to radiations, and the haematological findings in "luminizers". The historical aspects now so often neglected make very rewarding reading to a new generation (which includes the reviewer). On the other hand where the non-physicist tyro must be inducted firmly and accurately, for instance, in the basic physical laws and in definition of physical units of dose, the presentation is disappointing. Neither the concepts nor the expression of them are made clear. For instance (p. 17) "Since some forms of radiation differ in their biological effects another unit, the rem, has been introduced for comparison in this respect with the rad; and still another the R.B.E., for comparing the biological destructiveness of the different types of radiation." It is doubtful if R.B.E. can be considered in theory a unit; certainly it is not in practice, and the rem is purely a calculation, the product of rad and R.B.E.

If, alas, it is not possible to get the perfect primer from a single author, a second edition written jointly with a health physicist having the gifts of balance and clarity of exposition might produce it.

JOHN F. LOUTIT

Paraplegie Traumatiche. Edited by Africoa Serra and Ettore Tranquilli-Leali. (Pp. xxxvii + 964; 279 figures, 37 colour plates. Price not given) Rome: Edizione I.N.A.I.L. 1959.

This book is attractively presented and, as is necessary for most readers, has an excellent opening in which the anatomical and physiological implications of traumatic paraplegia are made clear.

The chapters on ossification of the spine, its blood supply, and the lymphatic system are very clear.

Having classified the various lesions which may occur, the writers proceed to consider, one by one, their sequelae. A chapter on oedema after spinal injury is of much interest. The writers note that the oedematous fluid contains large amounts of phosphatides and conclude that this is evidence of increased capillary permeability which, associated with paralytic vasodilatation, explains much of the condition. The rapid appearance of decubitus ulcers is due in part to local ischaemia and may result in a superimposed infection. As muscular atrophy progresses, the patient has an increasing handicap and this atrophy is aggravated by the lack of movement and thus, lack of nutrition. Protein katabolism keeps well ahead of the anabolic processes and, to

reduce this handicap, the diet should be carefully adjusted in quality as some of the amino-acids may soon be markedly deficient. Certain authorities have given intravenous protein hydrolysates for some days after the injury, finding that this improves appetite and is generally helpful. Similarly, insulin has also been given to improve the appetite. Although much is written about the care of the bladder after spinal injury, the writers admit that the mechanisms governing its action are often difficult to understand. In discussing the care of the bowel, they emphasize that a high residue diet gives far better results than one of low residue, which is often prescribed since the patient is regarded as being more ill than injured.

One case here reported is of unusual interest. A man fell from a tree and was found to have a lateral dislocation of L.1 on L.2. Though completely paralysed at first, he was up and about after two months with little to show apart from some weakness in the right foot. Part of L.1 had sheared off but the cord was clearly almost intact.

The biochemical changes seen in this condition are described very fully.

The difficulty of making an immediate diagnosis of injury to the cord may be great since several conditions, other than this, may suggest that its functions are locally impaired. Hernia of a disc may occur. If cervical, it may cause pain similar to that of torticollis, extending to the shoulder and arm. Or the cord may be suffering from commotion, contusion or shock, but without division of its essential parts.

The writers consider that androgens such as testosterone are of considerable value in treatment, both by assisting osteoblastosis and by their general stimulant effect. Some value is attached to Bogomoletz' serum in speeding up the healing of bedsores. For these pedicle grafts have also been used.

In the chapter on laminectomy the work of Böhler receives a tribute while chordotomy is well described and well illustrated.

The chapters on training specialists in this field and on the equipment needed are interesting. To judge from the illustrations, there is no lack of good apparatus and no lack of skill in its use.

The reviewer, when working with Italian doctors during the war, had the impression that pre-operative measures and post-operative care, if understood, were rarely used to the same degree as in Anglo-Saxon countries. Judging from this book, a great improvement has occurred in Italy in this respect.

G. C. PETHER

Pneumoconiosis Abstracts, Vol. III, 1951-1955. Reproduced from the *Bulletin of Hygiene* by permission of the Honorary Managing Committee of the Bureau of Hygiene and Tropical Diseases. (Pp. viii + 376. 65*s.*) London: Pitman Medical Publishing Co. 1959.

This most useful volume is a sequel to the two preceding volumes which were published in 1953 and 1954. These volumes contain abstracts which first appeared in the *Bulletin of Hygiene*; the first volume covered the years 1926 to 1938, the second 1939 to 1950, and the present volume covers the years 1951 to 1955 inclusive. The set of three volumes therefore contains a comprehensive collection of abstracts of the important papers published in this field during a period of 30 years.

In addition to abstracts on the various forms of pneumoconiosis, abstracts of articles are included which deal with standards of air dustiness, with concentrations of dust from various processes, with technical methods of measurement of dust, and with the study of the physical properties of dusts and of their chemical and mineralogical characters.

All persons concerned with the study and control of dust diseases will find these volumes an invaluable source of information.

The latest volume is a good example of how useful the photographic method of reproduction can be.

J. G. GILSON.

Books Received

(Review in a later issue is not precluded by notice here of books recently received.)

Guide to Hygiene and Sanitation in Aviation. (Pp. 51; 18 figures. 3*s.* 6*d.*). London: H.M.S.O.; Geneva: World Health Organization. 1960.

Elongation of Low Back Pain. By George H. Hassard and Charles L. Redd; Foreword by Harvey E. Billing and R. S. Minsker. (Pp. xvi + 78; 47 figures. 36*s.*). Oxford: Blackwell; Springfield: Thomas. 1959.

Die Asbestose des Lungen: genese-Klinik-Röntgenologie. By H. Bohlig, G. Jacob, and H. Müller. (Pp. viii + 166; 137 figures. DM66.-). Stuttgart: Thieme. 1960.

Data Sheets on Dust Collectors. (Pp. 38 + index; illustrated; 30*s.*). Sheffield: British Steel Castings Research Association. 1960.

Air Sampling Instruments. (Illustrated; $7.50). Cincinnati: American Conference of Governmental Industrial Hygienists. 1960.

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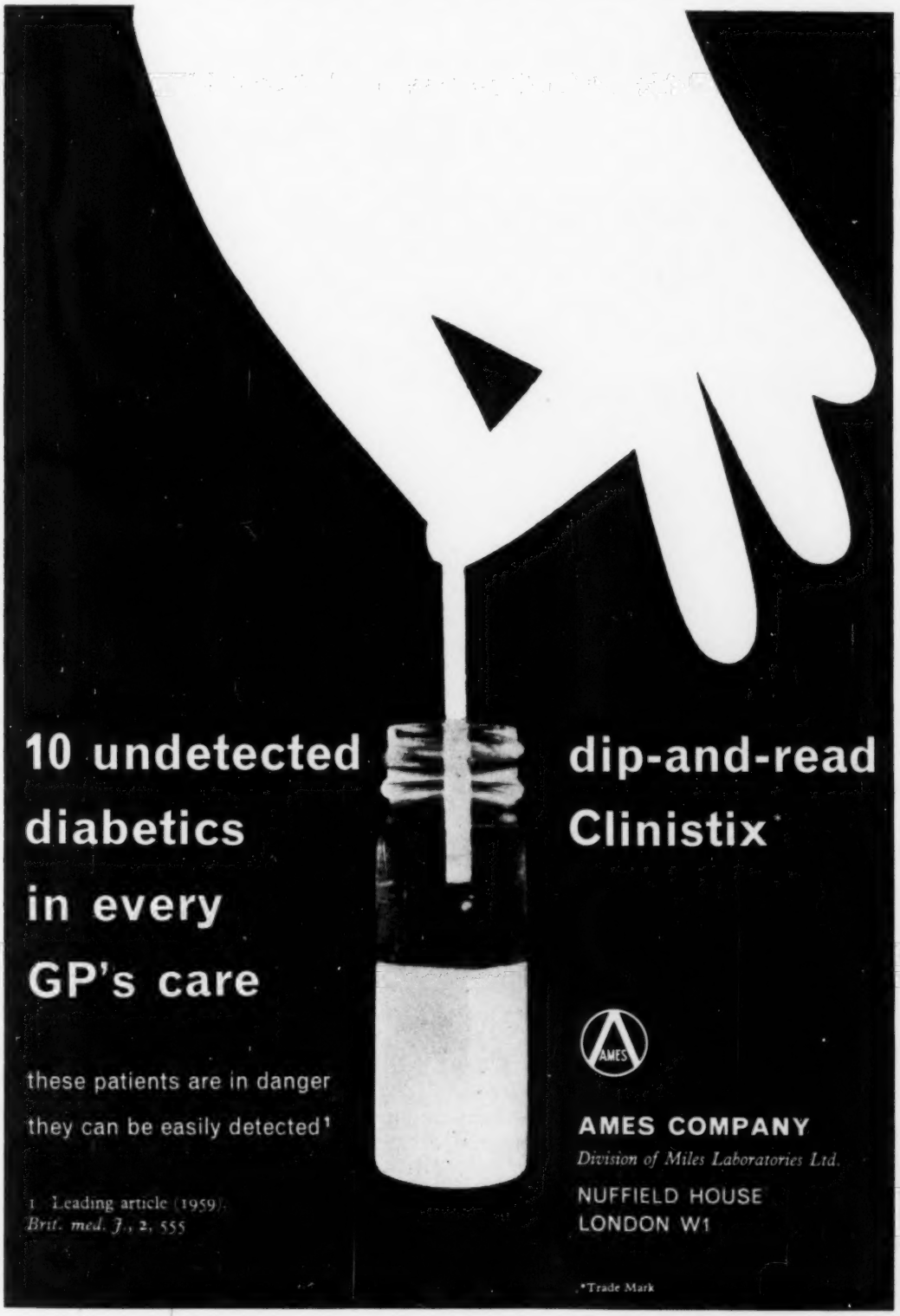
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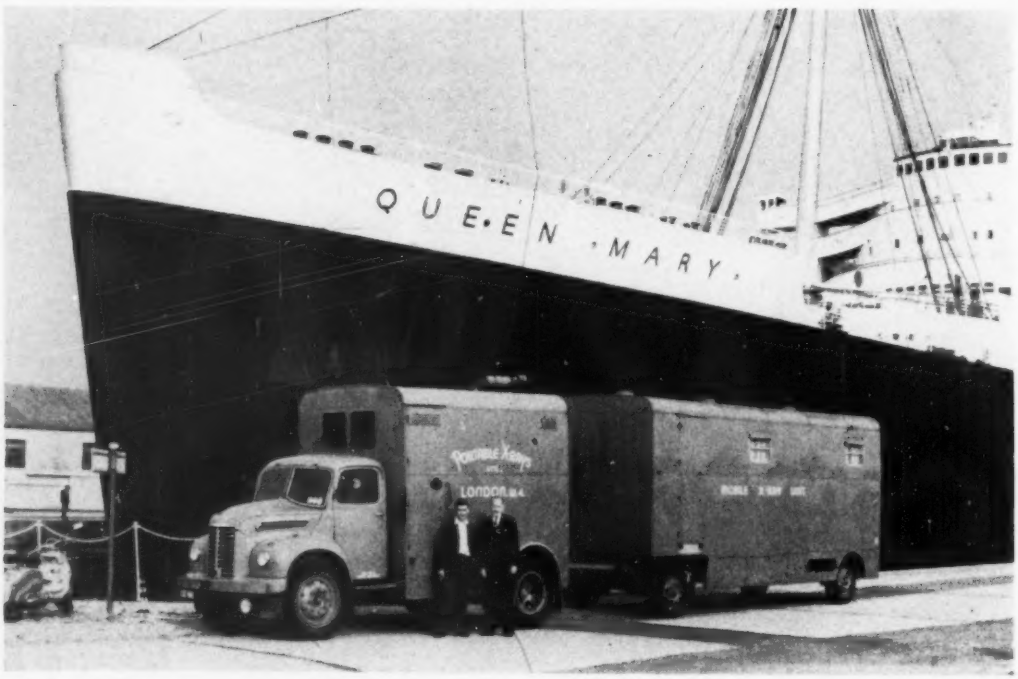

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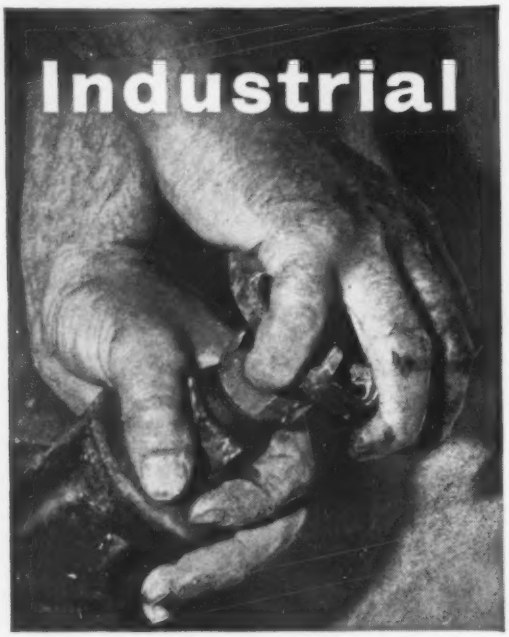

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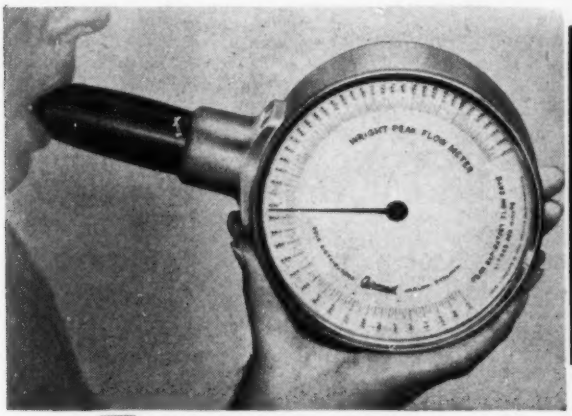

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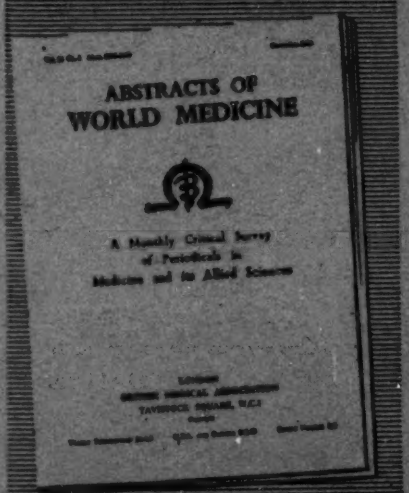

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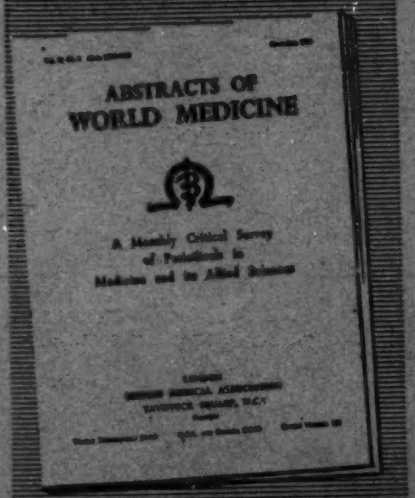

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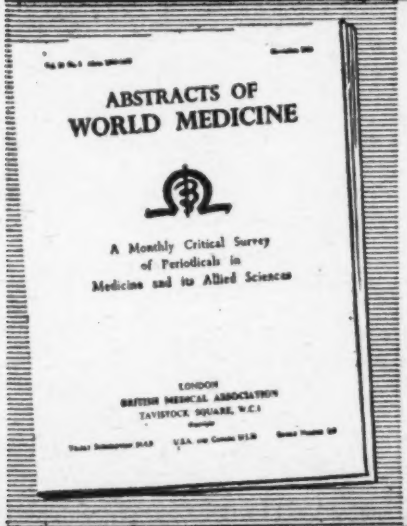

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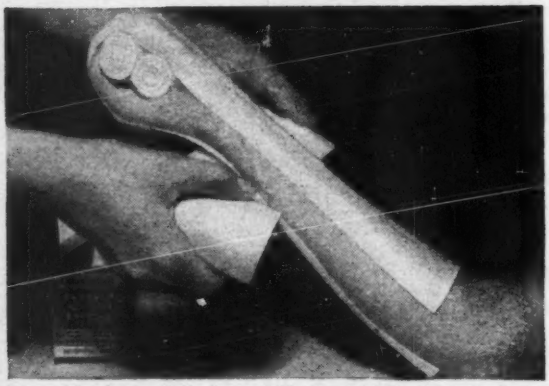

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